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The changing epidemiology of *Burkholderia* species infection at an adult cystic fibrosis centre

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Abstract

Background: This study reviews the impact of changing infection control practices at the Manchester Adult Cystic Fibrosis Centre (MACFC) upon the epidemiology of *Burkholderia* species infections.

Methods: We reviewed strain and genomovar typing of all available *Burkholderia* isolates at our centre between 1983–2006.

Results: The incidence/prevalence of infection with *Burkholderia* species between 1983–1990 was below 5%/9% each year. There was a rise in incidence/prevalence of *Burkholderia* species between 1991 and 1994 with a peak of 16.3%/31.2% in 1992. Following complete cohort segregation, the incidence has fallen to below 3% for all but one year and the prevalence has gradually reduced to 9.3% in 2005. Currently, there is an increase in the prevalence to 10.6% for the first time since 1994, predominantly due to patients with unique infections transferring into the unit from referring centres. The presence of unique strains now exceeds transmissible strains for the first time since 1991.

Conclusions: Infection control measures including patient segregation have controlled spread of transmissible *B. cenocepacia* strains, but not the acquisition of unique strains. Unique strains of *Burkholderia* species now account for the majority of new infections at the Manchester Adult Cystic Fibrosis Centre.

Keywords: Burkholderia cepacia complex; Epidemiology; Infection control

1. Introduction

The *Burkholderia cepacia* complex (Bcc) encompasses a group of inherently resistant organisms with complex taxonomy. The organisms were first described as pulmonary pathogens in cystic fibrosis (CF) in the late 1970s and early 1980s and were originally known as *Pseudomonas cepacia* [1]. The first detailed description of Bcc in CF was published in 1984 [2]. The name *Burkholderia cepacia* replaced *Pseudomonas cepacia* in 1992 with the creation of the new genus *Burkholderia* [3]. In 1997 a seminal paper revealed that organisms previously biochemically identified as *B. cepacia*, comprise different genomovars [4], a name used at that time to describe genomic *Burkholderia* species lacking a recognizable diagnostic phenotype. Currently, at least ten different Bcc species are recognised with more likely to follow [5]. In the past 20 years, the growing importance of the Bcc has been recognized by significant advances in our knowledge of the epidemiology and clinical role of Bcc and other related organisms.

Bcc organisms have been recognized as capable of being transmitted between CF patients since the 1980s [2,6,7,8]. The majority of strains of Bcc associated with cross-infection are *B. cenocepacia* strains [7]. Indeed, the epidemiology of Bcc and in particular the intercontinental spread of the highly transmissible *B. cenocepacia* ET12 lineage, has served as a model for the investigation of patient-to-patient transmission with regard to

Abbreviations: Bcc, *Burkholderia cepacia* complex; BMI, Body Mass Index; CF, Cystic Fibrosis; FEV1, Forced expiratory volume over one second; MACFC, Manchester Adult Cystic Fibrosis Centre; PFGE, Pulsed-field gel electrophoresis.

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other CF pathogens. Evidence indicates that Bcc transmission (but not acquisition from the natural environment) can be significantly reduced by patient cohort segregation/isolation [9]. It is therefore accepted universally by CF centres that patients infected with Bcc organisms should be segregated from other CF patients.

The potential for transmission of Bcc between patients is thought be dependent upon a number of variables. Certain strains, especially the *B. cenocepacia* lineage known as ET12, appear to be inherently more transmissible [7,9]. Social contact, especially of a prolonged nature, can pose a risk [6,7]. Individual host factors may play a role [10,11]. Evidence also exists for direct and indirect environmental transmission [12]. Airborne dissemination of the Bcc has been identified during physiotherapy treatments [13].

The transmission of Bcc species has been described within CF centres in many countries. There are also regional variations in such strains with the predominant transmissible strain identified in the United Kingdom and Canada being *B. cenocepacia* ET12. This strain has been reported to "superinfect" patients who have harboured another Bcc [14,15]. Based on such evidence, many centres have further enhanced their infection control policies to segregate patients with Bcc infection according to Bcc strain type.

Past studies substantially and repeatedly demonstrated worse clinical outcomes in patients chronically infected with Bcc than those CF patients without Bcc infection [16–19]. These observations are highly influenced by the morbidity and mortality associated with *B. cenocepacia* infection [17–20]. "Cepacia syndrome", a necrotising pneumonic illness with very high mortality and limited successful therapeutic interventions [2,9,2,21,22], is particularly associated with *B cenocepacia*, but can occur with other Bcc species [15,22,23]. *B. cenocepacia* infection is also associated with higher rates of mortality and morbidity post-bilateral sequential lung transplantation [24–26]. Two recent studies have suggested that infection with some Bcc species may not confer the same degree of increased morbidity and mortality as *B. cenocepacia* [18,19].

Transient infection with Bcc species has been demonstrated [4,9,19]. However there is no known reliable, proven eradication therapy for early Bcc infection. Thus, the most important step in the control of Bcc infection within a CF centre remains adherence with infection control measures that address the potential of cross-infection through patient-to-patient spread.

The Manchester Adult CF Centre (MACFC) is a large adult CF centre in the North-West of England. It currently provides care to 300 adults with CF. This centre has previously documented poorer clinical outcomes in those patients with *B. cenocepacia* infection [19]. This paper aims to outline the experience in responding to a change in epidemiology of *Burkholderia* species infection in patients treated within our centre.

2. Method

All cases of respiratory infection by Bcc species or other *Burkholderia* species, including *B. gladioli*, have been recorded at our centre since 1983. Microbiological surveillance for cross-infection with *Burkholderia* species has been performed at our centre since 1991. We have a policy of sending sputum for culture on a *B. cepacia* selective media to the local microbiological laboratory at each clinic contact with the patient. All *Burkholderia* species isolated are sent to the Edinburgh CF Microbiology Laboratory and Strain Repository for confirmation of species status within the Bcc by PCR-based methods, and strain typing (fingerprinting) by pulsed-field gel electrophoresis (PFGE). Isolates whose PFGE profiles were identical or differed by up to four DNA bands were considered to be clonal and to represent strain clusters.

In 2001, all Manchester Bcc isolates stored in the repository from 1983 onwards were identified to species level and strain typing performed by PFGE. Since 2001, all isolates have been prospectively identified and typed as a matter of routine clinical practice.

Infection control measures to prevent Bcc cross-infection were first implemented in 1991. Initially in 1991, patients with *Burkholderia* species infection were cohorted into different areas of the inpatient facility (partial cohorting). Specifically, patients with *Burkholderia* species infection were admitted to inpatient beds on the opposite side of the corridor to non-*Burkholderia* species infected patients. There was continued patient mixing within a day-room facility on the ward and within areas such as the radiology department. Patients with *Burkholderia* species infection attended separate outpatient clinics to other CF patients.

From November 1993 onwards, patients with *Burkholderia* species infection have been cohorted into separate wards to non-Bcc infected patients and each inpatient has their own single room. Patients with *Burkholderia* species infection have also continued to attend a different outpatient clinic (complete cohort segregation).

During 2000, a policy of isolation was introduced for patients infected with all *Burkholderia* species. This policy involves patients not having any contact with other patients, either at an inpatient or outpatient level. This is achieved by patients being admitted to single rooms during admissions and attending outpatient appointments and being immediately isolated within their own clinic room.

Data relating to species identification and strain typing of all available *Burkholderia* species isolated at our centre from the years 1983 to 2006 inclusive were reviewed from our database. The MACFC Bcc database holds information including dates of acquisition of Bcc infection, strain type, date of referral to the centre, and deaths.

A precise definition of "transmissible" and "epidemic strain" is difficult. For the purposes of this review, *Burkholderia* isolates exhibiting similar PFGE patterns and displaying evidence of cross-infection involving two or more CF patients are termed transmissible strains [7]. Unique strains refer to those strains with a unique profile.

3. Results

The incidence and prevalence of infection with *Burkholderia* species during the period 1983–1990 varied from 3 to 5% and 4 to 9% respectively (Fig. 1).

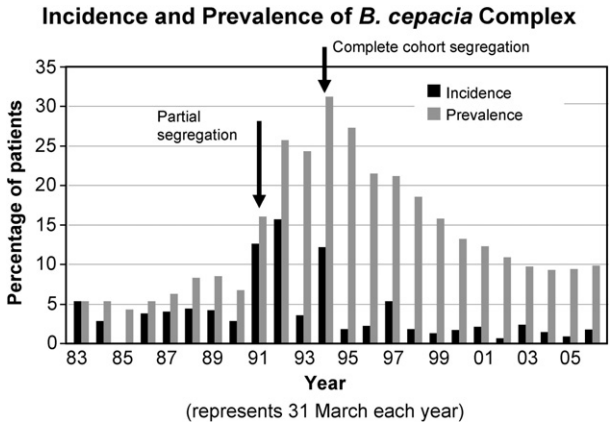

Fig. 1. Incidence and prevalence of *B. cepacia* complex infection at the Manchester Adult Cystic Fibrosis Centre, 1983–2006.

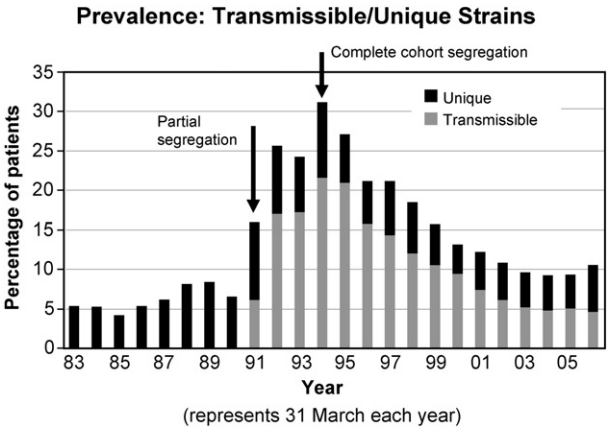

Fig. 3. Prevalence of transmissible and unique strains of *B. cepacia* complex infection at the centre, 1983–2006.

There was a rise in incidence and prevalence of *Burkholderia* species between 1991 and 1994. The peak incidence of 16.3% was seen in 1992 and the peak prevalence was 31.2% in 1994 (Fig. 1). Prior to 1991, there was no evidence of *Burkholderia* cross-infection at the MACFC. The first transmissible strain emerged in 1991 after a Manchester patient returned from a CF holiday camp in North America [7].

Following the introduction of complete cohort segregation at the end of 1993, the incidence of *Burkholderia* species infection has fallen to below 3% for all but one year (Fig. 1) and the prevalence has gradually reduced to 9.3% in 2005 (Fig. 1).

Fig. 2 highlights the incidence of infection with transmissible and unique strains of the *Burkholderia* species at the MACFC. The incidence of transmissible infection peaked in 1992 at 16.3% and has reduced to less than 2% for each year since 1994. In contrast, the incidence of infection with unique strains of *Burkholderia* species has fluctuated between 1983 and 2006.

Fig. 3 demonstrates that the prevalence of transmissible infections peaked at 21.6% in 1993/94 and fell to <5% in 2005. In contrast, the prevalence of unique strains peaked at 9.7% in 1991, fell to 4.3% in 2005 and during 2006 increased to 6%. In 2006, an increase in the total prevalence of all *Burkholderia* strains to 10.6% was seen for the first time since 1994 (Fig. 1). This increase can be explained by patients with unique infections transferring into the centre from other referring centres (Fig. 3). The prevalence of unique strains of *Burkholderia* species now exceeds that of transmissible strains for the first time since 1991 (Fig. 3).

In the past 12 years since complete cohort segregation, within the centre, there have been 6 cases of new infection with transmissible *B. cenocepacia* strains (all ET12) and 13 with unique strains of *Burkholderia* species (Fig. 4). The 6 cases of new transmissible *B. cenocepacia* have included 2 patients who chose not to comply with infection control policies and continued to socialise with other patients who harboured this pathogen, and 2 cases of superinfection prior to the implementation of isolation by strain type. Additionally, there was an accidental meeting of 2 patients in a lift that could explain another new case of transmissible infection. The reason for the other case of new acquisition of a transmissible strain remains unclear.

For the past 6 years, there has been just 1 case of new infection with a transmissible *B. cenocepacia* strain and 9 cases of new infection with unique strains of *Burkholderia* species amongst established patients of the centre (Fig. 4). The case of new infection with a transmissible strain was superinfection by

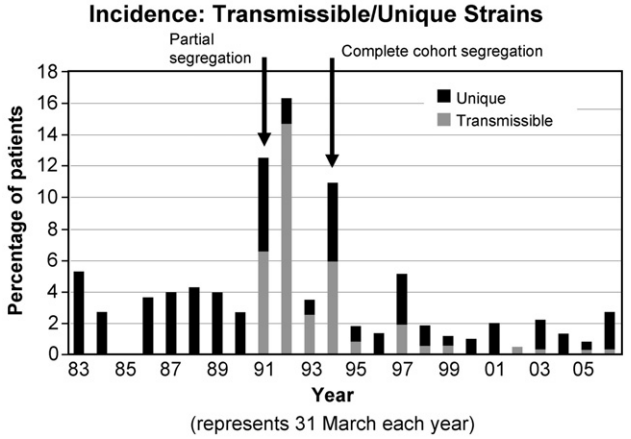

Fig. 2. Incidence of transmissible and unique strains of *B. cepacia* complex infection at the centre, 1983–2006.

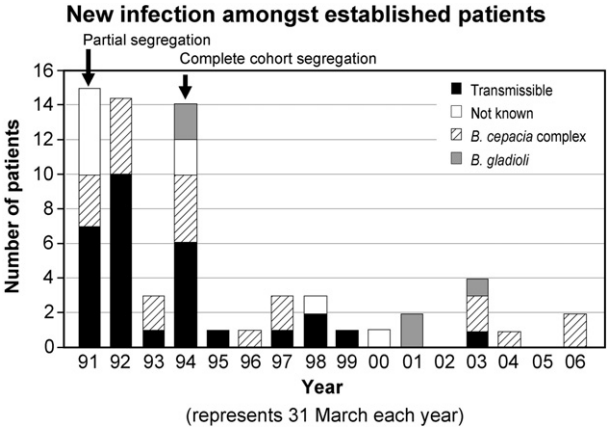

Fig. 4. New infection amongst established patients at the centre, 1991–2006.

the highly transmissible *B. cenocepacia* ET12 strain in a patient harbouring *B. multivorans* who chose not to adhere to the centre's infection control policies by socialising with another patient infected with the epidemic *B. cenocepacia* strain. Of the 9 new unique infections, 5 were *Burkholderia multivorans*, 1 was *Burkholderia cenocepacia* (not ET 12) and 3 were *Burkholderia gladioli*.

4. Discussion

This study highlights a number of important issues in relation to *Burkholderia* species infections at CF centres. The importance of a microbiological and molecular surveillance program, the success of complete cohort segregation in controlling spread of a transmissible strain and a subsequent change both in the proportion of Bcc infections represented by transmissible strains and other non-*cenocepacia* strains are supported by the study.

The introduction of partial cohorting in 1991 was in response to a sharp increase in both the incidence and prevalence of *Burkholderia* species infection within the centre. When it was noted that the incidence and prevalence of *Burkholderia* species infections continued to increase, the surveillance program allowed for an appropriate modification of the infection control policies of the centre. This led to the introduction of complete cohort segregation in November 1993. Patients with Bcc infection were segregated into different outpatient clinics and different wards, after the CF centre was relocated to another hospital. In more recent times, an "isolation" approach has been adopted. This involves patients not having any contact with other patients admitted to the ward or within the outpatient area.

Evidence of cross-infection between CF patients and evidence of superinfection with transmissible strains of *Burkholderia* species prompted annual surveillance of all strains and instigation of complete cohort segregation in clinics and isolation on the wards of the MACFC [14,15]. Concurrently, the UK CF Trust produced national guidelines highlighting the importance of patient education surrounding infection control and infection control surveillance policies and procedures [27].

If pro-active microbiological surveillance, in particular accurate species identification and molecular typing had not been in place, further spread of the transmissible strain would likely have occurred. The obvious benefits of such a surveillance program have been demonstrated by this study. Molecular typing to confirm or exclude clonality allowed for the recognition that transmissible strains of *Burkholderia* species were responsible for the increased incidence and prevalence within the centre. It is therefore important that any surveillance programme includes molecular typing of bacterial isolates. Furthermore, the recent recognition of intercontinental spread by another highly transmissible *B. cenocepacia* strain (known as *B. cenocepacia* strain PHDC) [28] and reported cross-infection with *B. dolosa* in North American [8] have highlighted that all CF centres should be alert to possible emergence of other transmissible Bcc strains within their units, and these can only be discovered by continued molecular microbiological surveillance programs.

Surveillance programs are only of benefit if appropriate changes in infection control policies can be introduced once a change in epidemiology of an infectious pathogen has been recognised. The first systematic review of the efficacy of segregation and isolation of patients with Bcc infection was published in 2005 [29]. It observed that there are no randomized controlled trials in the area; however, most authors recommend the segregation of patients with Bcc infection from those without [29]. Similarly, a recent review paper from the Italian Cystic Fibrosis Research Foundation performed a literature search to examine published evidence to support segregation and isolation for infection control in Bcc and *P. aeruginosa*-infected patients [30]. The paper found a paucity of controlled, prospective data in the area [30]. It did however conclude that the existing retrospective data does support segregation of patients with pathogens such as Bcc [30]. Notably, this paper did not include Danish data, collected between 1970 and 1987, which showed a fall in the incidence of new chronic *Pseudomonas aeruginosa* infection from 17% in 1976–1980 to 3% in 1986–1987 [31,32]. This change in the epidemiology of new chronic *P. aeruginosa* infection was seen after the introduction of elective intravenous antibiotics but before the introduction of early treatment of intermittent *P. aeruginosa* infection [31]. Our experience with complete cohort segregation and later isolation, lends further support to the body of literature demonstrating the efficacy of segregation in preventing patient to patient spread of Bcc infections.

Prevention of acquisition of Bcc infection is of paramount importance for a number of reasons. The inherent multiresistance of the pathogen and the lack of evidence of successful eradication mean that therapeutic options are more limited and challenging [33]. The poorer clinical outcomes demonstrated in Bcc infections, particularly those caused by transmissible strains of Bcc, further highlights the reason for prevention of acquisition [17–20].

This review of the MACFC's experience has demonstrated that complete cohort segregation and isolation infection control policies have controlled the spread of transmissible strains. It has reinforced that complete cohort segregation has lead to a change in the proportion of Bcc infections represented by transmissible strains. It will be noted that cohort segregation has not affected the sporadic acquisition of unique strains from natural environments. Unique strains of *Burkholderia* species, in particular *Burkholderia multivorans* now account for the majority of new *Burkholderia* species infections within the unit.

The clinical challenges presented by an increase in unique strains remain uncertain. The clinical impact of infection with these unique strains may be different from the historical lessons learnt from the era of transmissible strains of *B. cenocepacia*. Transient infection is also more common with unique strains and hence a great proportion of the initial infections with *Burkholderia* species may not progress to chronic infection [4,9,19].

In summary, the importance of ongoing microbiological surveillance for transmissible pathogens has been reinforced by this review. The early detection of a change in the epidemiology of a pathogen allows the swift implementation of appropriate infection control policies to halt the spread of transmissible

pathogens. The effectiveness of complete cohort segregation and isolation as infection control policies in response to an increase of the prevalence of transmissible strains of *Burkholderia* species has been demonstrated. It remains to be seen what the clinical impact of the changing epidemiology of Bcc infection with a much greater proportion of unique strains of non-*B. cenocepacia* strains will have.

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