

# **EPIDEMIOLOGY OF NONTUBERCULOUS MYCOBACTERIA INFECTION IN CHILDREN AND YOUNG PEOPLE WITH CYSTIC FIBROSIS: ANALYSIS OF UK CYSTIC FIBROSIS REGISTRY**

Aaron I. Gardner, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom.

Elliot McClenaghan, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom.

Gemma Saint, Department of Child Health, University of Liverpool, United Kingdom and Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom.

Paul S. McNamara, Department of Child Health, University of Liverpool, United Kingdom and Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom

Malcolm Brodlie\*, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University and Department of Paediatric Respiratory Medicine, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom Newcastle upon Tyne, United Kingdom

Matthew F. Thomas\*, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University and Department of Paediatric Respiratory Medicine, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom Newcastle upon Tyne, United Kingdom

\*Equal contribution

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Corresponding author details: Malcolm Brodrie ([malcolm.brodrie@ncl.ac.uk](mailto:malcolm.brodrie@ncl.ac.uk)), MRC Clinician Scientist/Honorary Consultant in Paediatric Respiratory Medicine, Level 3, Clinical Resource Building, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom, NE1 4LP.

40-word summary: *“The prevalence of NTM infection is increasing in children and young people with cystic fibrosis - there is an urgent requirement to establish the most effective strategies to prevent and treat NTM infection in the paediatric age group.”*

Running title: NTM infection in children with CF

## ABSTRACT

**Background:** Infection with nontuberculous mycobacteria (NTM) is of growing clinical concern in people with cystic fibrosis (CF). The epidemiology of infection in children and young people remains poorly understood. We wished to investigate the epidemiology of NTM infection in the paediatric age-group using data from the United Kingdom CF Registry.

**Methods:** Data from 2010-2015 for children and young people aged <16 years (23,200 observations from 5,333 unique individuals) were obtained. Univariate analysis of unique individuals comparing all key clinical factors and health outcomes to NTM status was performed. Identified significant factors were used to generate a multivariate logistic regression model, which following step-wise removal generated a final parsimonious model.

**Results:** The prevalence of individuals with a NTM positive respiratory culture increased every year from 2010 (45 [1.3%]) to 2015 (156 [3.8%]). Allergic bronchopulmonary aspergillosis (OR 2.66, P =

$5.0 \times 10^{-8}$ ), age (OR 1.08,  $P = 3.4 \times 10^{-10}$ ) and intermittent *Pseudomonas aeruginosa* infection (OR 1.51,  $P = 0.004$ ) were significantly associated with NTM infection.

**Conclusions:** NTM infection is of increasing prevalence in the UK paediatric CF population. This study highlights the urgent need for work to establish effective treatment and prevention strategies for NTM infection in young people with CF.

**Key words:** Cystic fibrosis; nontuberculous mycobacteria; children; NTM; epidemiology.

## INTRODUCTION

Over 10,000 individuals have cystic fibrosis (CF) in the United Kingdom (UK) making it the most common inherited life-limiting condition.[1] More than 4,000 are children or young people under the age of 16.[1] The CF Trust maintains a detailed UK patient registry that records anonymised clinical data and health outcomes.[2] The registry is updated annually and captures information that covers over 90% of people with CF nationally.[1, 2] Despite the development of specialist care and incremental improvements in survival, lung disease still accounts for the substantial majority of morbidity and premature mortality in people with CF.[3] Susceptibility to respiratory infection with particular microbes is a key component of the pathology of CF lung disease and approaches that target the treatment or prevention of infection are a mainstay of clinical management.[3]

Infection with nontuberculous mycobacteria (NTM) has become a subject of increasing clinical concern in people with CF over the last 5 years.[4] NTM are environmental organisms found commonly in soil and water. Two groupings are most frequently isolated from people with CF, *Mycobacterium abscessus* complex and *M. avium* complex. Infection with *M. abscessus* specifically has been found to be associated with increased decline in lung function.[5, 6] Treatment of airway infection with NTM requires prolonged courses of multiple antibiotics, often for over 12 months, and

is associated with a significant treatment burden and frequent adverse effects.[4, 7] Furthermore, *M. abscessus* infection is regarded as a relative contraindication to lung transplantation in many centres.[8] There is also emerging evidence to suggest transmission of *M. abscessus* between individuals with CF.[9, 10]

There are varying estimates of the prevalence of NTM isolation in respiratory samples from people with CF that range from 3.7% in parts of Europe to 14% in the United States (US). [11, 12] Several reports have suggested an increasing prevalence over the last decade above that accounted for by improved screening and detection techniques.[5, 13-16] A previous European registry study of a combined adult and paediatric CF population identified age, allergic bronchopulmonary aspergillosis (ABPA), *Stenotrophomonas maltophilia* infection and use of bronchodilators, inhaled antibiotics or rhDNase to be associated with NTM infection.[17] Specific knowledge of the epidemiology of NTM infection in children and young people with CF is particularly limited at present. Paradoxically it is in the paediatric age group where interventions and strategies to treat or prevent infection with NTM are likely to yield the greatest clinical benefits.

We analysed data from the UK CF registry to investigate the epidemiology of NTM infection in children and young people under the age of 16 between 2010 and 2015. This included trends in the prevalence of NTM infection, individual species isolated, demographic and clinical 'risk factors' in individuals isolating NTM, along with longitudinal analyses. This data and analyses will inform future clinical research relating to NTM infection in children and young people with CF.

## **METHODS**

### **Clinical Data and Research Ethics**

Annual review data submitted to the UK CF Registry database between 2010 and 2015 for patients up to the age of 16 (23,200 observations from 5,333 unique individuals) were obtained.

Supplementary Table 1 lists the variables obtained. Data lacking a unique identifying code, were excluded from the analysis (n=38).

Explicit written consent is obtained from individuals or their parents or guardians for their inclusion in the UK CF Registry. The registry is compliant with UK data protection legislation and subject to continued Research Ethics Committee approval. Data for this study were obtained by application to the CF Trust Research Registry Committee, who approved the application and released anonymised data in line with the existing registry ethics approvals.

### **Data Analysis**

The data were firstly cleaned and checked for duplicates. For each individual NTM positive status was defined using the specific registry field which is returned if an individual has had a positive NTM culture in the preceding year. Intrinsically, this was not whether an individual met the criteria for NTM related pulmonary disease (NTM-PD) but purely whether they had a positive culture in that 12-month period.[18] In the 2014 and 2015 registry censuses this field was expanded to collect more detailed data about NTM status including species, date of culture and treatment data. Individuals were tracked through the time period using their unique registry ID.

All unique individuals were then pooled for analysis of epidemiological risk factors predictive of NTM status. These included demographics (age, sex, anthropometric measurements), *CFTR* genotype, lung function, other respiratory microbiological status (*P. aeruginosa*, *Staphylococcus aureus* and *Burkholderia cepacia* – *S. aureus* and *P. aeruginosa* were subdivided in to 3 states – negative, intermittent - defined as 1-2 isolations in the last year or chronic - defined as 3 or greater isolations in the last year) and co-morbidities (CF-related diabetes or ABPA).

Following a standard approach, univariate non-parametric tests were used to assess predictive value and all significant predictors were then included in a multivariate logistic regression model. Step-

wise removal of non-significant factors was then undertaken to generate the final parsimonious model presented. For variables with multiple categorical states included in the multivariate model, e.g. *P. aeruginosa* status, an overall effect was estimated using the Wald test.

Next, the progress of patients NTM status was tracked over the whole time period to generate annual incidence, prevalence and potential response to treatment estimates. For patients who remained NTM positive or NTM negative for the duration of the study period, only their latest time point was included for analysis. Those with multiple classifications, i.e. those who developed or were cleared of NTM infection during the study period, were classified as NTM positive and data from their latest NTM positive time point was included for analysis.

Finally, descriptive data on NTM species and treatment were collated and explored for the 2014 and 2015 data extracts. All analyses were carried out using Microsoft Access 365, GraphPad Prism 6.05 and R 3.4.1 using the *nlme* package.[19]

## RESULTS

### **The prevalence of individuals aged 16 years and under with a positive respiratory culture for NTM increased year on year between 2010 and 2015**

The prevalence of individuals with a NTM positive respiratory culture in the UK CF Registry aged 16 and under increased every year from 2010 (45 [1.3%]) through to 2015 (156 [3.8%]) (Figure 1). An especially large increase in cases was observed between 2013 (83 [2.1%]) and 2014 (140 [3.6%]). Following the pooling of yearly cohorts the number of overall unique NTM cases was identified (288 from 5,333 [5.4%]).

### **Age, *P. aeruginosa* and ABPA are associated with NTM positive status**

Table 1 summarises the differences between those children and young people who had an NTM positive respiratory culture and those that did not. On average children who isolated NTM were

older (median 10 years vs. 6 years,  $P = 2.2 \times 10^{-16}$ ), were more likely to be positive for *P. aeruginosa* (45% vs 30%,  $P = 0.013$ ), *B. cepacia* (2.4% vs 0.9%,  $P = 0.013$ ) and to have ABPA (17% vs 4.7%,  $P = 2.2 \times 10^{-16}$ ).

No gender difference was seen, nor was a difference between *F508del* (c.1521 1523del) homozygotes or heterozygotes. Heterozygosity for the *W1282X* (c.3846G>A) mutation was statistically significantly associated with positive NTM status. However, given the scarcity of this (21 heterozygotes) and other rare mutations in the dataset the chance of statistical error was deemed too great for further analysis.

While on average individuals who had a respiratory culture positive for NTM had a lower body mass index (BMI) percentile (44.3 vs 53.4,  $P = 0.850$ ) and lower forced expiratory volume in 1 second ( $FEV_1$ ) percentile (81.3 vs 86.4,  $P = 0.286$ ) neither was statistically significantly different. No difference was seen between rates of *S. aureus*, *B. cenocepacia* and *B. multivorans* infection between the two groups. There was no statistically significant difference in the incidence of CF-related diabetes between the NTM positive and negative groups (3.8% vs 2.8%,  $P = 0.321$ ).

Following univariate analysis and step-wise logistic regression, age, *P. aeruginosa*, *B. cepacia* and ABPA status were incorporated into a multivariate model (Table 2 and Figure 2). In the final model increased age and ABPA were significantly associated with NTM status with a larger effect observed for ABPA (age OR 1.08, 95% CI 1.06-1.11,  $P = 3.4 \times 10^{-10}$  and ABPA OR 2.66, 95% CI 1.85-3.75,  $P = 5.0 \times 10^{-8}$  respectively). Intermittent, but not chronic, *P. aeruginosa* colonisation was also significantly associated (OR 1.51, 95% CI 1.14-1.99,  $P = 0.004$ ). *B. cepacia* was not significantly associated and hence removed from the final parsimonious model.

### **Incidence, prevalence and successful treatment markedly increased between 2013 and 2014**

By following individual patients through the registry longitudinally, it was possible to determine the incidence of new cases as a proportion. Between 2011 and 2013 approximately 40% (~26 cases per

year) of NTM positive individuals were new cases (Table 3 and Figure 3 a). As discussed above, a large increase in the overall number of NTM cases was observed between 2013 and 2014 which was accounted for by a large increase in the number of new cases arising that year (63% (88)).

We then assessed the outcomes for patients who did not carryover NTM positive status into the following years analysis based on the registry data. Between 2010 and 2012 approximately 2 (~4%) patients per year cleared NTM for the duration of the study (Table 4 and Figure 3 b). In 2013 and 2014 there was a marked increase in this number up to 16 (19.3%) and 33 patients (23.6%) respectively, however it is likely that some of this effect is due to the endpoint of existing data.

### **NTM treatment appears broadly consistent with published guidelines**

From 2014 the registry began including NTM typing information from patient isolates and treatment information where available. For both 2014 and 2015 *M. abscessus* (72 [51.4%] and 55 [35.3%] respectively) and *M. avium* (16 [11.4%] and 13 [8.3%] respectively) accounted for the majority of known infections (Figure 4 and Supplementary Table 2). A large proportion of samples lacked specific typing information in 2014 (46 [32.9%]) which increased in 2015 (86 [55.1%]).

A wide variety of therapies were employed in the treatment of NTM. Descriptive data is presented in Supplementary Table 3 on the different antimicrobials used. Treatments broadly followed accepted guidelines with amikacin preferentially used for the treatment of *M. abscessus* over *M. avium*. [4, 7] In a small number of cases ethambutol and rifampicin are recorded as having been used to treat *M. abscessus*, which is not in keeping with guidance and is likely to have been ineffective.

## **DISCUSSION**

We present data from the nationally representative UK CF Registry that show an increase in children and young people isolating NTM in respiratory cultures between 2010 and 2015. Over five years



there was a threefold increase in the prevalence of NTM positive cultures with approximately 5% of children and young people under 16 years of age included in the registry being NTM-positive at some point during the study period. *M. abscessus* complex and *M. avium* complex accounted for the overwhelming majority of isolates. Similar to other cohorts, age and ABPA status appeared significant predictors of NTM culture positivity, in addition to *P. aeruginosa* status.[17]

A major strength of this study is derived from the nationally representative longitudinal source data. The UK CF Registry is an internationally recognised resource with greater than 90% of individuals with CF in the UK included in the dataset. The methodology of data collection has remained consistent over the time period we report, meaning that we can have confidence that reporting bias should not be a factor in these estimates. Secondly, this dataset allows investigation and analysis of the epidemiology of NTM infection specifically in children and young people under the age of 16 and represents the largest paediatric cohort analysed in this regard. There are important biological differences as CF lung disease progresses through a spectrum from the early stages in children to advanced disease in adults. Furthermore, children and young people receive care in paediatric centres that may adopt different models of care from adult centres.

Conversely, the limitations of our study stem from the fundamental structure, as we had no direct control over reporting and are inherent to registry-based research. The registry does not record data on the frequency of sampling in patients or the sample types used. However, all UK centres delivering care are expected to adhere to the 2010 CF Trust guideline '*Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis*'. Furthermore, the '*Standards for the Clinical Care of Children and Adults with cystic fibrosis in the UK*' document published in 2011 states that all patients should have a respiratory sample cultured for NTM at least annually. It is possible however, that surveillance on only a yearly basis may lead to underestimation of the true prevalence. In some cases there was no recording of the individual species of NTM in the registry.

It is also important to state that the presence of positive respiratory cultures for NTM is not synonymous with NTM-PD as defined by the American Thoracic Society/Infectious Disease Society of America 2007 statement.[18] The diagnosis of NTM-PD requires multiple clinical criteria to be met and is beyond the scope of this study.

The question of whether the increase in prevalence of NTM represents a true rise in NTM-PD in UK children with CF or simply represents better detection is a vexatious one. Similar questions have arisen in virtually every epidemiological study of infection and the data we present cannot fundamentally differentiate between these two possibilities. Methods to culture and detect NTM in respiratory samples have developed over recent years. For example, a new selective NTM growth medium has been demonstrated to increase sensitivity of the detection of NTM, but this is only used in a minority of UK CF centres.[14, 20, 21] Over the same time period reports have suggested possible transmission of NTM, specifically *M. abscessus* complex, between individuals with CF despite the presence of routine infection control measures in CF centres which would provide a potential mechanism for the observed increasing prevalence.[9, 10, 22, 23]

Within our cohort we found associations with increasing age (OR 1.08,  $P = 3.4 \times 10^{-10}$ ), ABPA (OR 2.66,  $P = 5.0 \times 10^{-8}$ ) and *P. aeruginosa* status (intermittent OR 1.51,  $P = 0.004$ ) and risk of NTM positive respiratory samples. These were consistent findings over the different annual cohorts and were also found in the pooled analysis of all unique individuals. Viviani *et al.* reported similar associations with age and ABPA, but not *P. aeruginosa*, in multivariate analysis of European registry data from both children and adults with CF combined.[17]

It is conceivable that all 3 identified risk factors in our study represent surrogate markers of increased lung destruction or damage which has been postulated to increase an individual's vulnerability to NTM acquisition in individuals without CF.[24, 25] Advancing age is also associated with an inherent increase in duration of time at risk of exposure. There may also be ecological interactions within the lung microbiome that predispose to co-acquisition of *P. aeruginosa*,

Aspergillus species and NTM. Furthermore host immune function is likely to be relevant to these risk factors. In people with chronic obstructive pulmonary disease, the use of inhaled corticosteroids has been found to be a risk factor for NTM infection.[26] ABPA is usually treated with corticosteroids and it is conceivable that there is a similar association in people with CF.

Our finding of a difference in the association between NTM status and intermittent and chronic *P. aeruginosa* status is counterintuitive. The distribution of the confidence intervals of the chronic status (Figure 2), however, strongly favours an effect and the overall class effect (combining both chronic and intermittent status) is significant. We suspect in larger populations this difference would likely disappear. It is worth noting that in the UK CF Registry classification of *P. aeruginosa* status is based on the number of positive respiratory samples during the last 12 months (negative, intermittent - defined as 1-2 isolations or chronic - defined as 3 or greater isolations), irrespective of whether or not the individual is maintained on chronic anti-pseudomonal suppression therapy for example nebulised antibiotics.

Our results highlight that NTM infection appears to be increasing significantly in the UK paediatric CF population. An observation made anecdotally and expressed readily at CF clinician meetings over the last 5 years. These data make a compelling argument for urgent investment in research of NTM infection in children and young people. The advances we have seen in clinical outcomes in CF have largely come from innovations and improvements in paediatric CF care and similarly by addressing NTM infection in childhood the greatest potential gains can be made. Our data lead us to conclude that two areas in particular need urgent focus and collaboration. Firstly, precise, detailed epidemiological data on NTM infection in childhood needs to be obtained so that strategies to prevent acquisition can be developed. Secondly, urgent randomised trials of anti-microbial therapies directed against *M. abscessus* complex and *M. avium* complex in children and young people are required.

## ACKNOWLEDGEMENTS

We are grateful to the Cystic Fibrosis Trust UK Research Registry Committee for approving and facilitating our access to the data analysed in this research.

## FUNDING

This work was supported by the Medical Research Council (UK) [grant number MR/M008797/1 Clinician Scientist Fellowship to M.B.]; and the National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals NHS Foundation Trust and Newcastle University. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

## CONFLICTS OF INTEREST

AIG, EM, GS and PSM: None. MB: Not related to this work: investigator-led research grants from Pfizer and Roche Diagnostics. Honoraria for talking at educational meetings paid to Newcastle University from Novartis, TEVA and Roche Diagnostics. Travel and accommodation for educational meeting from Boehringer Ingelheim. MFT: Not related to this work: investigator-led research grant from Pfizer.

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**Table 1 - Summary of merged registry data 2010-2015 and univariate analysis of risk factors for NTM positive cultures**

Variable	All		NTM		NTM Negative		P Value
	n (%)	Median (Quartiles)	n (%)	Median (Quartiles)	n (%)	Median (Quartiles)	
Subjects	5,333 (100)		288 (5.4)		5,045 (94.6)		
<b>Demographics</b>							
Male	2,717 (50.9)		138 (47.9)		2,579 (51.1)		0.554
Female	2,615 (49)		150 (52.1)		2,465 (48.9)		
Age	5,333 (100)	6 (2-12)	288 (100)	10 (7-12)	5,045 (100)	6 (2-12)	2.2x10 <sup>-16</sup>
Height Percentile	5,110 (95.8)	112.2 (79.6-142.6)	282 (97.9)	133.9 (117.7-145.9)	4,828 (95.7)	110 (78.7-142)	0.020
Weight Percentile	5,235 (98.2)	19.3 (10.9-34.9)	281 (97.6)	28.8 (21.5-37.6)	4,954 (98.2)	18.6 (10.6-34.7)	0.420
BMI Percentile	3,846 (72.1)	52.8 (28.2-76.1)	262 (91)	44.3 (22.1-70.48)	3,224 (63.9)	53.48 (28.5-76.53)	0.850
<b>Genotype</b>							
<i>F508del F508del</i>	2,704 (50.7)		164 (56.9)		2,540 (50.3)		0.418
<i>F508del/Other</i>	1,968 (36.9)		89 (30.9)		1,879 (37.2)		0.452
<i>Other/Other</i>	661 (12.4)		35 (12.2)		626 (12.4)		0.469
<b>Lung Function</b>							
FEV <sub>1</sub>	2,541 (47.6)	1.64 (1.2-2.2)	64 (22.2)	1.5 (1.2-1.9)	2,728 (54.1)	1.7 (1.2-2.2)	0.991
FEV <sub>1</sub> % Predicted	2,271 (42.6)	85.9 (73.4-97.5)	76 (26.4)	81.3 (68.2-94.1)	2,986 (59.2)	86.4 (74.3-97.8)	0.286
<b>Respiratory Microbiology</b>							
<i>S. aureus</i>	1,298 (24.3)		85 (29.5)		1,213 (24)		
Chronic	319 (6)		23 (8)		296 (5.9)		0.093
Intermittent	979 (18.4)		62 (21.5)		917 (18.2)		0.103
<i>P. aeruginosa</i>	1,640 (30.8)		130 (45.1)		1,510 (29.9)		0.013*
Chronic	505 (9.5)		45 (15.6)		460 (9.1)		8.65x10 <sup>-06</sup>
Intermittent	1,135 (21.3)		85 (29.5)		1,050 (20.8)		1.93x10 <sup>-05</sup>
<i>B. cepacia</i>	54 (1)		7 (2.4)		47 (0.9)		0.013
<i>B. cenocepacia</i>	13 (0.2)		2 (0.7)		11 (0.2)		0.111
<i>B. multivorans</i>	25 (0.5)		3 (1)		22 (0.4)		0.143
<b>Comorbidities</b>							
ABPA	285 (5.3)		49 (17)		236 (4.7)		2.2x10 <sup>-16</sup>
CFRD	153 (2.9)		11 (3.8)		142 (2.8)		0.321

Summary statistics for merged data. 38 data points lacking a unique identifying code were removed from the analysis, leaving a final count of 5,333 subjects. Univariate analysis comparing each factor to NTM status was performed and P values presented. Significant factors (highlighted) were included in the final multivariate analysis. \*By Wald test,  $\chi^2 = 8.6$ ,  $P = 0.013$ . Tested prior to inclusion in multivariate model. FEV<sub>1</sub> – Forced expiratory volume exhaled at the end of the first second of forced expiration, *S. aureus* - *Staphylococcus aureus*, *P. aeruginosa* – *Pseudomonas aeruginosa*, *B. cepacia* - *Burkholderia cepacia*, *B. cenocepacia* - *Burkholderia cenocepacia*, *B. multivorans* - *Burkholderia multivorans*, ABPA - allergic bronchopulmonary aspergillosis, CFRD – cystic fibrosis related diabetes.



**Table 2 – Odds ratios and significance for multivariate model**

Variable	Odds Ratio	95% CI	P Value
ABPA	2.656	1.854 - 3.748	$5.0 \times 10^{-8}$
<i>P. aeruginosa</i> Intermittent	1.511	1.139 - 1.990	0.004
<i>P. aeruginosa</i> Chronic	1.275	0.875 - 1.825	0.195
Age	1.084	1.057 - 1.111	$3.4 \times 10^{-10}$

Odds ratios, 95% CI and P values for ABPA, chronic and intermittent *P. aeruginosa* and age from the multivariate model are displayed. ABPA - allergic bronchopulmonary aspergillosis, *P. aeruginosa* – *Pseudomonas aeruginosa*.

**Table 3 – NTM origin**

Year	New Cases (%)	Carryover (%)	Re-infection (%)	Total
2010	45 (100)	0 (0)	0 (0)	45
2011	26 (41.9)	36 (58.1)	0 (0)	62
2012	26 (38.2)	41 (60.3)	1 (1.5)	68
2013	27 (32.5)	54 (65.1)	2 (2.4)	83
2014	88 (62.9)	45 (32.1)	7 (5.0)	140
2015	76 (48.7)	76 (48.7)	4 (2.6)	156
Total (%)	288 (52.0)	252 (45.5)	14 (2.5)	554

Origin of NTM cases per year, data visualised in Figure 3 a.

**Table 4 – NTM patient outcomes**

<b>Year</b>	<b>Lost to analysis (%)</b>	<b>Cleared for duration (%)</b>	<b>Later re-infection (%)</b>	<b>Lost to Registry (%)</b>	<b>Total</b>
2010	6 (13.3)	1 (2.2)	2 (4.4)	0 (0)	9
2011	12 (19.4)	3 (4.8)	6 (9.7)	0 (0)	21
2012	9 (13.2)	3 (4.4)	2 (2.9)	0 (0)	14
2013	17 (20.5)	16 (19.3)	4 (4.8)	1 (1.2)	38
2014	26 (18.6)	33 (23.6)	0 (0)	5 (3.6)	64
<b>Total</b>	<b>70</b>	<b>56</b>	<b>14</b>	<b>6</b>	

NTM patient outcomes per year, data visualised in Figure 3 b.

## FIGURE LEGENDS

### Figure 1 – NTM prevalence by year

The prevalence of NTM in CF patients increased year on year with a particularly large increase observed between 2013 and 2014. Following data merge, the number of unique cases overall (288, 5.4%) was identified. Values in brackets show percentage of individuals positive for NTM per year.

### Figure 2 – Odds ratios for multivariate model

Odds ratios and 95% CI for ABPA, chronic and intermittent *P. aeruginosa* and age from the multivariate model are displayed. Values are shown in Table 2.

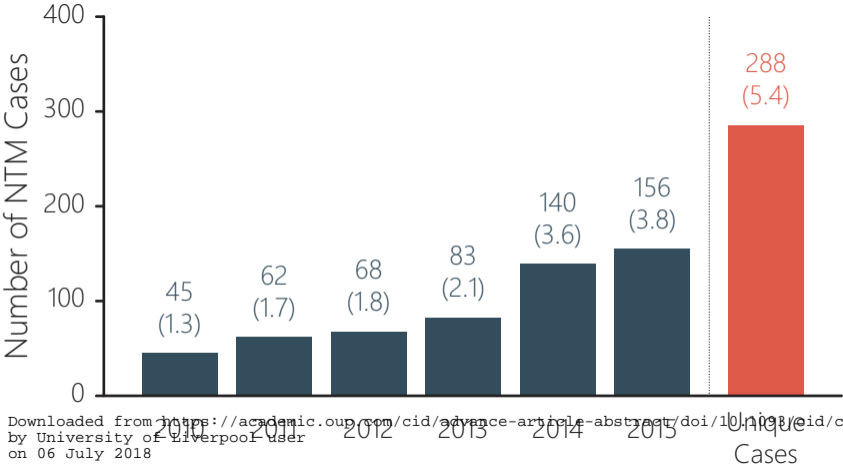
### Figure 3 – NTM origin and patient outcomes

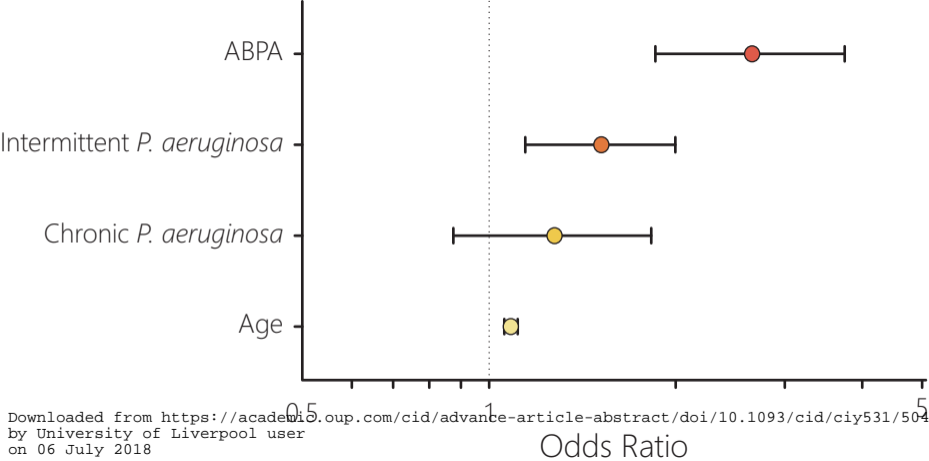
a) Individual patients were tracked through the registry and the source of infection graphed. A large increase in the total number and percentage new cases was observed between 2013 and 2014. Values are shown in Table 3.

b) Patient outcomes for those who didn't carryover NTM positive status into the following years analysis were also determined. A large increase in those who cleared NTM for the remainder of the assessment period was observed for 2013 and 2014. Values are shown in Table 4. Lost to registry refers to patients who should have remained available for analysis, but lacked registry data for later years for unknown reasons. Lost to analysis refers to patients who became older than 16 and so were no longer included in the analysis.

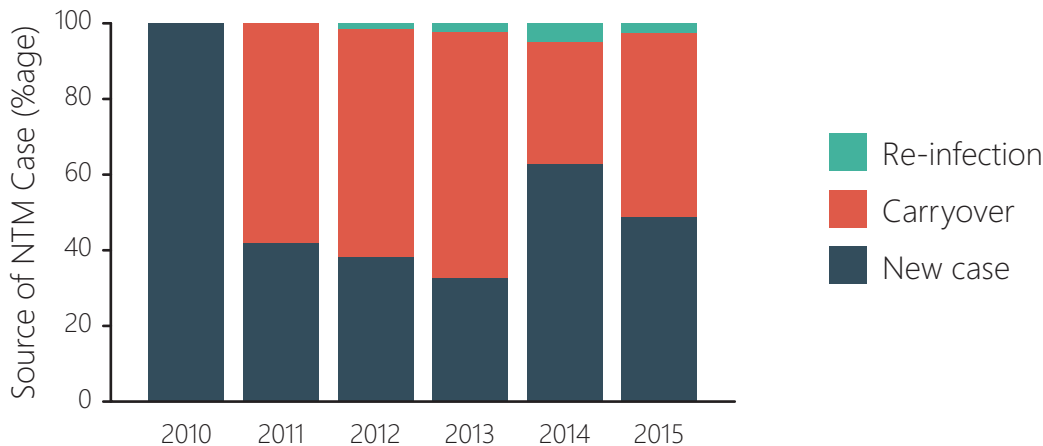
### Figure 4 – Specific strain information 2014 - 2015

For 2014 and 2015 the registry introduced NTM typing information. Some variation between years was observed, especially in relation to the number of unknown cases. *M. abscessus* and *M. avium* accounted for the majority of cases for each year. Values shown in Table 5.

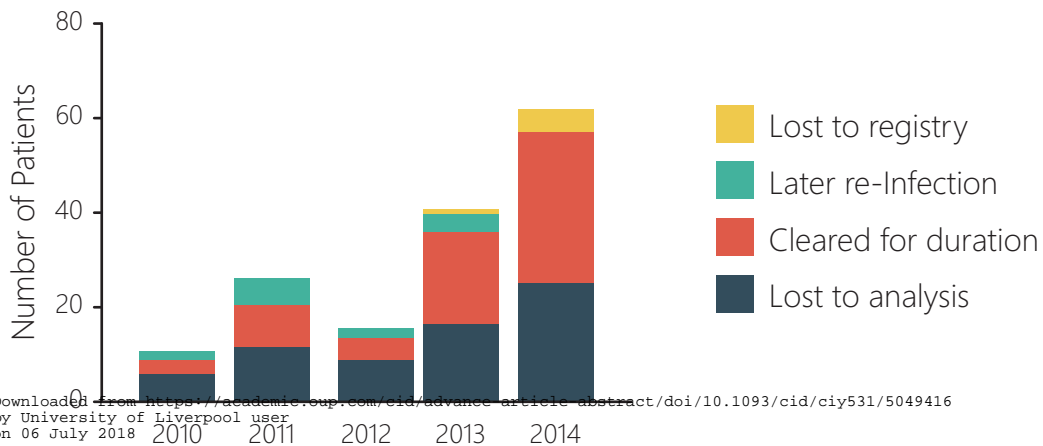




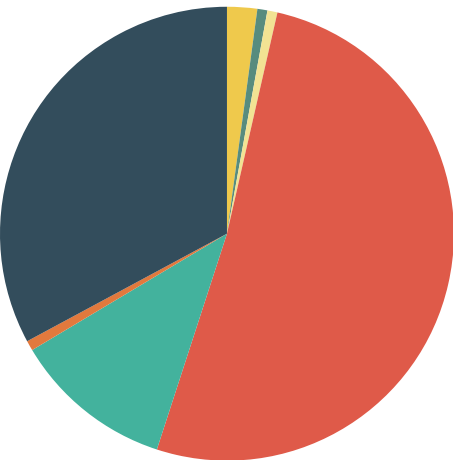
a)



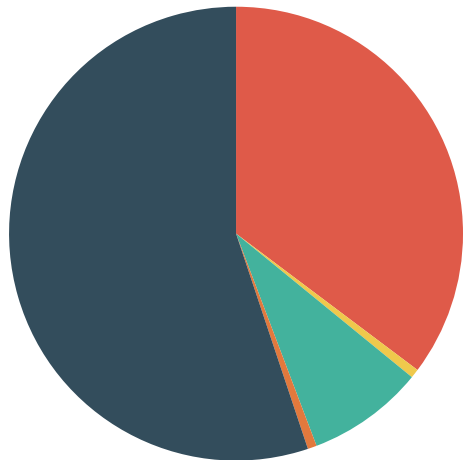
b)



2014



2015



*M. abscessus* + *M. avium*



*M. abscessus* + *M. chelonae*



*M. abscessus* + Unknown



*M. abscessus*



*M. avium*



*M. kansasii*



Unknown