Cystic Fibrosis why we're here

Research in focus

Pseudomonas aeruginosa infection in cystic fibrosis

Fighting for a Life Unlimited

Foreword

Cystic fibrosis (CF) causes thick, sticky mucus to build up in the airways. This prevents the body from being able to effectively remove bacteria from the airways, which can cause serious infections.

One type of bacteria that can cause a serious infection in people with CF is called *Pseudomonas aeruginosa (P. aeruginosa).* Once *P. aeruginosa* gets into the airways of someone with CF, it can adapt itself to grow and survive there extremely well. These adaptations can make CF infections extremely difficult to treat. If they're not treated effectively, infections can result in permanent damage to their lungs and can even shorten their lives.

People with CF spend a lot of time each day taking antibiotics and other medicines to stay well. From time-to-time they get a sudden worsening of their health, which is treated with extra antibiotics. When this happens people may need time off school or work and will feel unwell from the infection and the medicines themselves.

New medicines called CFTR modulators have transformed the lives of many people with CF, improving lung health and reducing the number of new infections they develop. However, even if someone can benefit from these drugs, research shows they will still require treatments for existing, long-term *P. aeruginosa* infections[1]. More effective medicines for CF infections of *P. aeruginosa* are urgently required for everyone living with CF, whether or not they're receiving CFTR modulators.

The Cystic Fibrosis Trust has invested over £2.6 million in research to develop more effective medicines for *P. aeruginosa* since 2013. A central theme of this research is trying to understand how the bacteria can adapt itself to grow and survive so well in the CF airways.

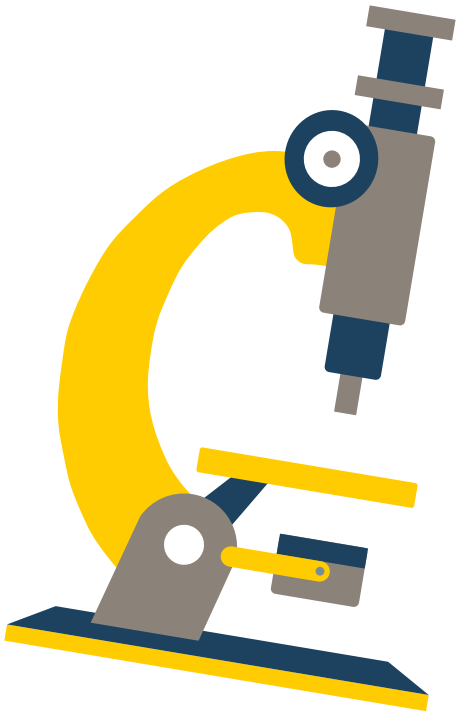
In this report we highlight two research programmes that are working to understand how and why *P. aeruginosa* adapts itself to the lungs of people with cystic fibrosis. Both programmes are ongoing, but the results so far give us hope for new and better treatments for this devastating infection in the future.

Dr Lucy Allen
Director of Research

Since 2013 we've spent

2.6 million

on research into *Pseudomonas aeruginosa* infection



What is CF?

Cystic fibrosis is a rare, inherited condition that affects around 10,600 people in the UK. It is caused by a defective gene called CFTR, which causes thick, sticky mucus to build up in the internal organs, especially the lungs and digestive system. This results in long-term infections and inflammation in the lungs, and in the digestive system, blockages, bloating and difficulty breaking down food. Some adults with CF may also develop CF-related diabetes (CFRD) and forms of arthritis, osteoporosis and liver problems that are related to having cystic fibrosis.

Lung infections in people with CF

People with CF are at risk of several different types of lung infections caused by bacteria, fungi and viruses. We are funding research into one of the most common and serious CF infections, caused by the bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*).

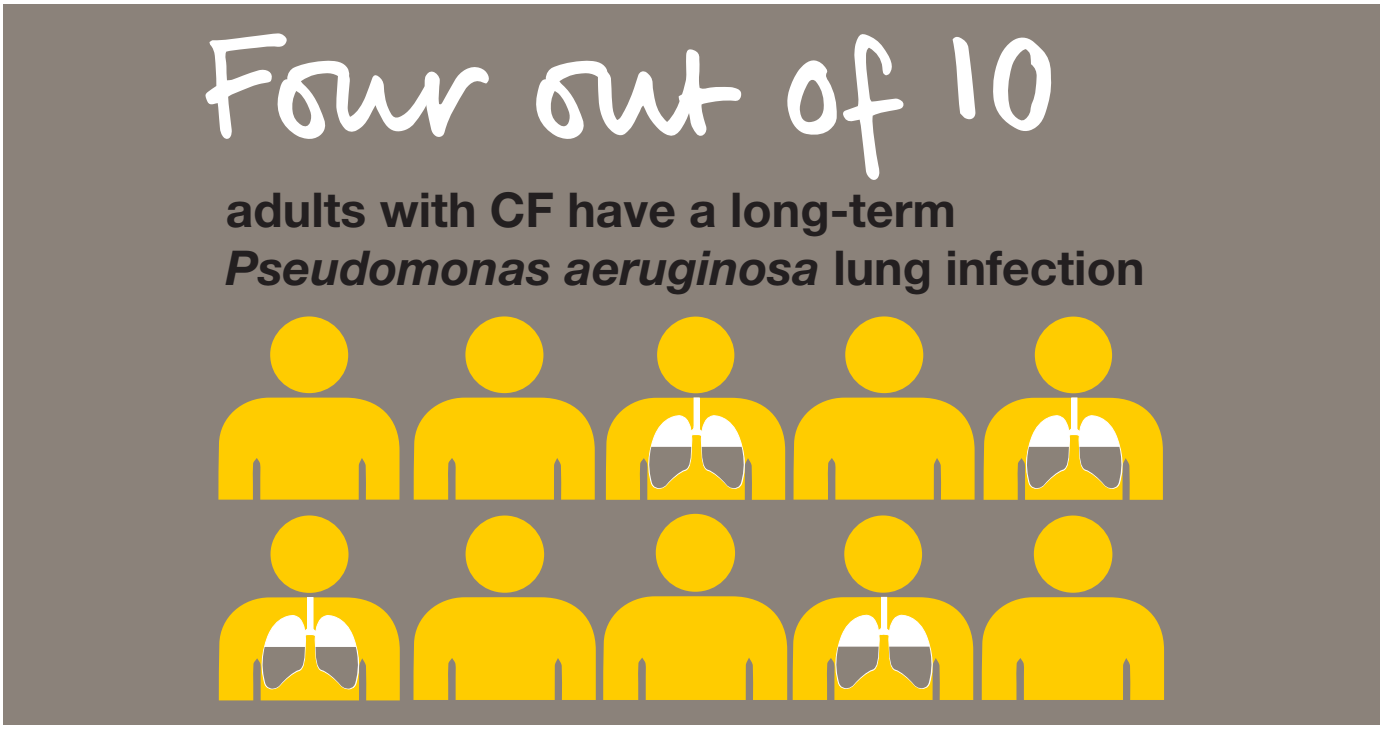
People with CF often develop their first *P. aeruginosa* infection in childhood, followed by a number of recurring infections as they get older. These infections become harder to completely clear (eradicate) from the lungs, and the focus of treatments becomes the management of long-term (chronic) infections. Four out of 10 adults with CF are currently living with chronic *P. aeruginosa* infections[2].

Long term infections of *P. aeruginosa* are treated with daily antibiotics, to try and control the infection and to reduce any damage it may cause to the lungs. When people with CF get a flare-up of infection known as an exacerbation, extra antibiotics are given. These might be fortnight-long courses of intravenous (IV) antibiotics, often with unpleasant side effects. The side effects can vary according to which antibiotics are given, but can include diarrhoea and extreme tiredness. IV treatments can be done during a hospital stay or at home. These treatments for exacerbations and the side effects they cause can create massive disruption to the lives of people with CF and those around them.

Many *P. aeruginosa* infections are even becoming resistant to the strongest antibiotics available. If the infections are left untreated, they can cause permanent lung damage, meaning people are more breathless and have less energy to do day-to-day activities.

Ultimately, a lack of effective antibiotic medicines can sadly shorten the lives of people with cystic fibrosis. People with CF identified more effective treatments for *P. aeruginosa* infections as a top health priority in a survey in 2017[3].

As well as causing serious lung infections in people with CF, *P. aeruginosa* can also cause serious skin and urinary tract infections in people who don't have cystic fibrosis. More effective medicines to treat all forms of *P. aeruginosa* infections are urgently needed. In 2017 the World Health Organisation published a list of bacteria that posed the greatest threat to human health and for which new treatments were most urgently needed. *P. aeruginosa* was in the 'critical' bacteria group, the top priority on this list.[4]



Cystic fibrosis can impact every aspect of your life. From the big decisions to planning small things. It takes out the spontaneity. When I get a flare-up of infection, life pauses: from when I start to feel ill, during the two weeks of treatments and then for quite a while after the treatment as I recover."

Ellie, 40, who has cystic fibrosis


Ellie

Studying evolution to find new ways to treat infection

Like the coronavirus that causes COVID-19, bacteria, fungi and viruses all have the ability to constantly alter themselves to create new 'variants'. This is known as evolution. The reason why bugs alter themselves or adapt is to improve their chances of survival – and lots of different factors affect this.

Some 'survival factors' are about basic needs. For example, the bugs might change their diet or adapt to survive in different temperatures.

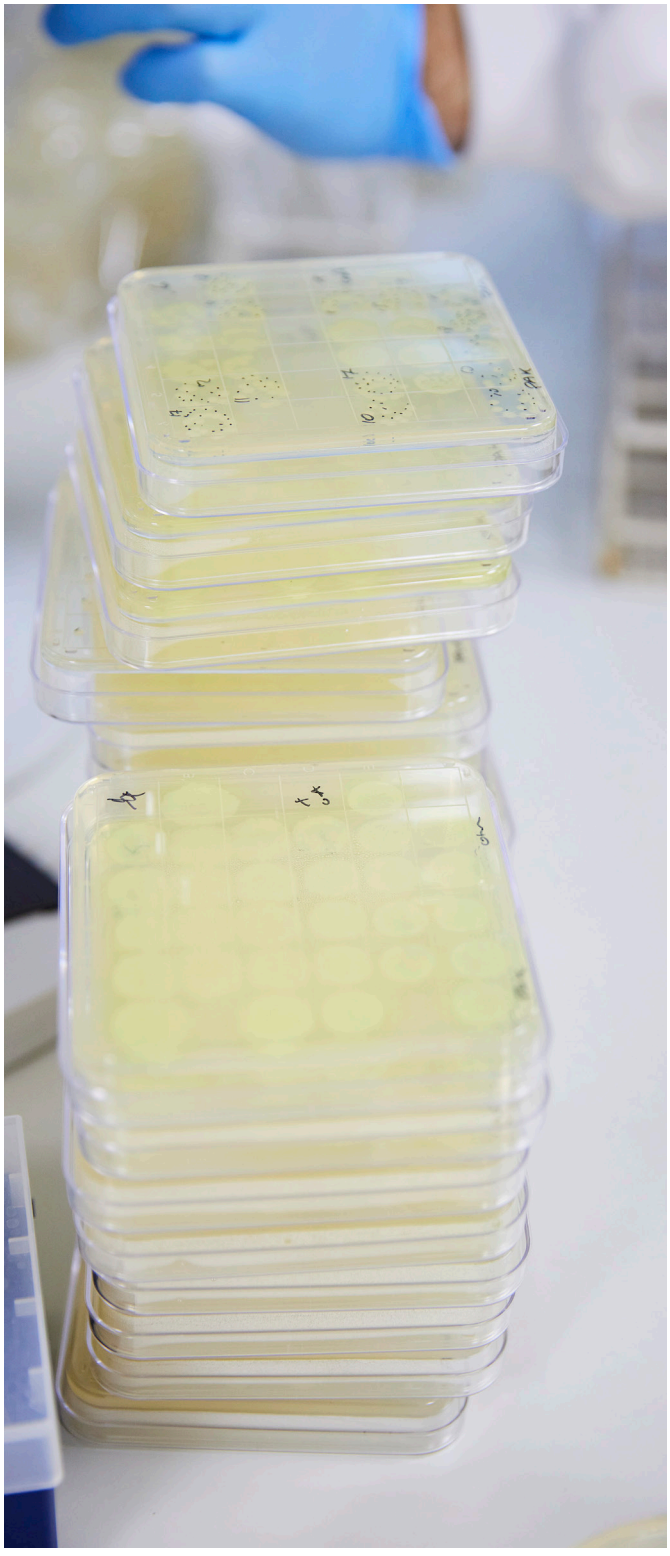
Others are about self-defence. The bug might need to defend itself against the body's immune system, against other bugs in the same environment, or against antimicrobial treatments.

Collectively, these adaptations may lead to a more aggressive infection as well as making the infection harder to treat.

The way that bacteria evolve is by changing their DNA. Each DNA change is random, like rolling a dice. As DNA is the genetic code, the changes lead to changes in the bacteria's genes. Each change might give the bacteria an advantage or a disadvantage, depending on their environment. For example, the bacteria might become resistant to certain antibiotics.

The bacteria with the more advantageous changes are more likely to grow and survive than the bacteria whose changes put them at a disadvantage.

Researchers are studying bacterial genes to understand how the bacteria are adapting to the lungs of people with cystic fibrosis. This will provide important information on how to treat *P. aeruginosa* CF infections more effectively.



What is the Trust doing?

Cystic Fibrosis Trust-funded researchers are investigating how bacteria evolve within the CF airways to find more effective ways to treat *P. aeruginosa* infection.

How *P. aeruginosa* changes in the CF airways

Dr Joanne Fothergill at the University of Liverpool is studying *P. aeruginosa* infections in the nose and sinuses of people with cystic fibrosis. She aims to understand more about how and when *P. aeruginosa* adapts to the CF airways. The Trust is funding this research in collaboration with the charity Action Medical Research through our Venture and Innovation Award (VIA) scheme.[5]

P. aeruginosa first enters the body via the nose and throat and then moves into the sinuses. This area of the body is known as the upper respiratory tract. Scientists know from previous research studies that *P. aeruginosa* begins to adapt to the CF airways within the upper respiratory tract before the infection reaches the lungs[6,7]. However, they don't yet know how this happens.

Dr Joanne Fothergill

Dr Fothergill and her colleagues want to identify early genetic changes in *P. aeruginosa* during infection in the upper respiratory tract. Their research could lead to new, more effective ways to treat *P. aeruginosa* infection in people with CF in the future.

The team have identified several specific changes that affect how *P. aeruginosa* survives in the CF airways and how it defends itself against antibiotic treatment. The results of one of these genetic changes has been shared with other researchers in the form of a scientific publication[8] and studies on other genetic changes are being completed before being written for publication.

"We discovered one of the changes that *P. aeruginosa* makes to its DNA when it grows in the CF lung makes the bacteria better able to survive there. The genetic change enhances its ability to attach to lung cells and improves its ability to provide resistance against the body's attempts to remove it."

Dr Joanne Fothergill, University of Liverpool

The effects of *P. aeruginosa* adaptation for the CF lung

Dr Martin Welch from Cambridge University is leading our Strategic Research Centre (SRC) to understand how *P. aeruginosa* has adapted to live in the lungs of people with CF, such as how it functions and the nutrients it uses. This will help researchers in the future find new ways to treat the infection.

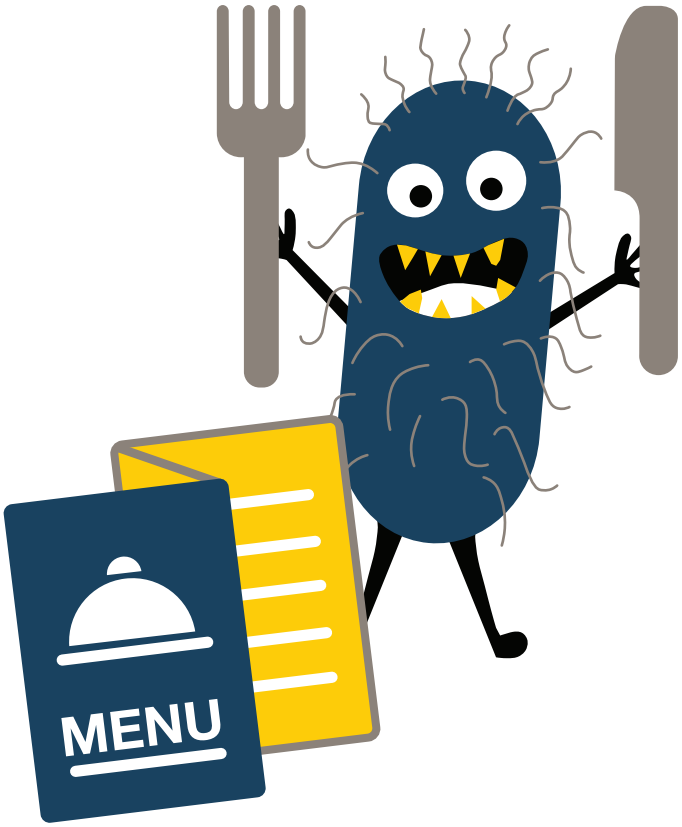
Every time *P. aeruginosa* makes a change to its genes as it adapts to growing and surviving in the CF airways, the way the bug functions changes. These changes in function are caused by changes to the chemical reactions taking place in the bacteria.

As you read this, there are hundreds of chemical reactions taking place in your body. These reactions are collectively known as 'metabolism', and they are essential to keep us alive. In the same way, there are lots of chemical reactions taking place in bacteria, to allow them to grow and survive. Antibiotics are designed to prevent the growth and survival of bacteria by blocking the most important of these reactions.

However, current antibiotics only work on a small proportion of them. That's why scientists are currently working to find new chemical reactions for future medicines to block.

In their Trust-funded SRC programme, Dr Martin Welch and an international team of researchers are working on a comprehensive set of studies, investigating what nutrients are required by *P. aeruginosa* to grow and survive in the CF airways[9].

Dr Martin Welch



They are also exploring how its metabolism changes as *P. aeruginosa* adapts to living in the lungs of someone with CF and whether all variants of the bug have the same nutritional requirements – whether they can eat the same things on the 'menu'.

"If you just use a single approach towards addressing a biological problem, you'll get an answer, but sometimes it won't be the whole picture, so it's very important that you use a selection of complementary approaches. We've got the world's top experts working on this Strategic Research Centre programme."

Dr Martin Welch, University of Cambridge

So far researchers working on the SRC in Denmark and Germany have independently shown that there are differences in the metabolism of *P. aeruginosa* when grown in the lab in conditions that mimic the environment in the lungs of someone with CF, compared to someone who doesn't have cystic fibrosis.

They've done this by looking at the nutrients *P. aeruginosa* is using and the waste products of its metabolism respectively. Looking at what *P. aeruginosa* pushes out of the bacteria as waste tells scientists how it uses nutrients to grow and survive.

The early results show that different waste products are produced by *P. aeruginosa* growing in people with CF, compared to variants only grown in the lab. The German research group found that the *P. aeruginosa* grown in the lungs of people with CF used specific types of nutrients.

The next step for both research groups is to determine what is causing these differences in metabolism. They will do this by analysing how often these *P. aeruginosa* genes are used within the bacteria. Their results will help us learn how we can treat infections more effectively.

"It would be reassuring to know that you can grow a new bug and it's not going to cause a huge drop in lung function because you're able to get rid of it. I haven't really thought about what it would mean to me to have better antibiotics as having lung infections is just something I've lived with."

Chloe, 26, who has cystic fibrosis

Chloe

We're funding lots of innovative research to understand how and why *P. aeruginosa* adapts itself to survive so well in CF airways. Although both research programmes described here are still at relatively early stages, they are important in laying the foundations. Future scientists and clinicians will be able to build on this knowledge to develop a better armoury of drugs to treat the complex lung infections that affect everyone with cystic fibrosis.

References

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