# Cystic Fibrosis why we're here

## Research in focus

Antimicrobial resistance in cystic fibrosis

Fighting for a Life Unlimited

## Foreword

In 1970 the average survival for children born with cystic fibrosis (CF) was below 20 years old.[1] Fifty years later, for a child born with CF today, the average predicted survival is 49.[2] During this time, access to effective antimicrobial drugs has made a significant contribution to people with CF living longer. However, there are infections that are becoming increasingly hard to treat as the bugs that cause them are becoming resistant to the antimicrobial drugs available. To overcome this resistance, we need to understand the bugs that cause CF infections and develop new antimicrobial drugs to combat them.

We are delighted to be working with world-leading scientists within our UK CF Innovation Hub at the University of Cambridge, who have been developing innovative and cutting-edge lab-based research programmes to tackle antimicrobial resistance (AMR). We hope that the development path of potential drugs from this programme, and from other biotechnology and biopharmaceutical companies working in the area, will be made easier by the work of the CF Syndicate in AMR – a facilitated partnership between the Cystic Fibrosis Trust and Medicines Discovery Catapult. The CF Syndicate in AMR was created to address challenges in CF antimicrobial discovery and development, in order to accelerate translation to the clinic and to ultimately bring better treatment options to people affected by cystic fibrosis.

Antimicrobial resistance is a global health concern[3] that, if left unresolved, could turn routine operations into life-threatening procedures. Advances made in developing new antimicrobial drugs for people with CF will benefit the global effort to combat antimicrobial resistance.

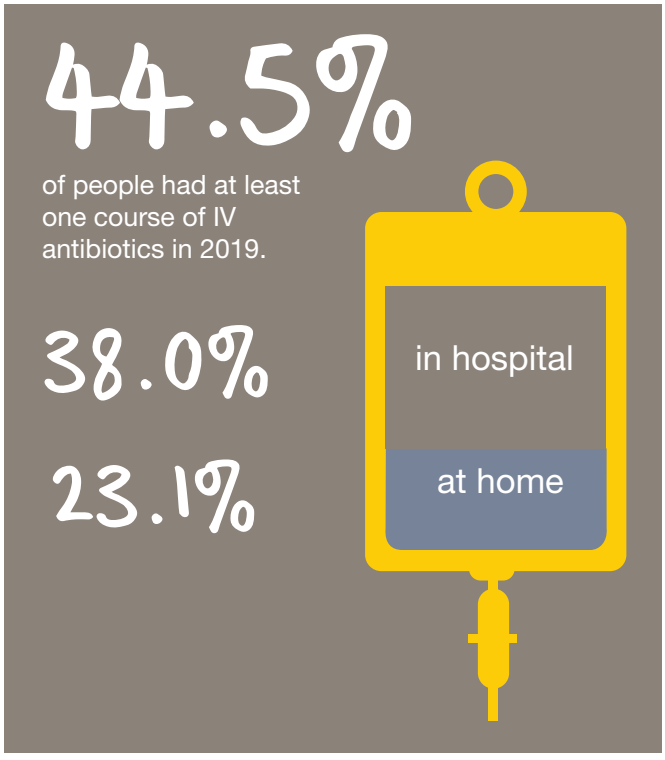
Dr Paula Sommer, Head of Research, Cystic Fibrosis Trust

## What is CF and how does it affect the body

Cystic fibrosis is a devastating condition that affects over 10,600 people in the UK. It is caused by a defective gene called 'CFTR', which controls the movement of salt and water in and out of cells. As a result of the defect, the internal organs – especially the lungs and digestive system – become clogged with thick, sticky mucus, resulting in chronic infections, inflammation in the lungs and difficulty digesting food. Some adults with CF may also get cystic fibrosis-related diabetes (CFRD), arthritis, osteoporosis and liver problems.

## Lung infections in people with cystic fibrosis

People with CF are susceptible to a number of different types of lung infections, caused by bacteria, fungi and viruses. Cystic fibrosis care is very dependent on the use of antimicrobials, particularly antibiotics (antibacterial drugs) for the treatment of these infections. Antibiotics are used proactively to control the extent and harmfulness of existing bacterial infections, as well as treating flare-ups of sudden dips in lung health known as exacerbations. It is common for people with CF to spend weeks in hospital several times a year for intravenous (IV) antibiotic treatment and monitoring. In 2019, 44.5% of people with CF received at least one course of IV antibiotics.[2]

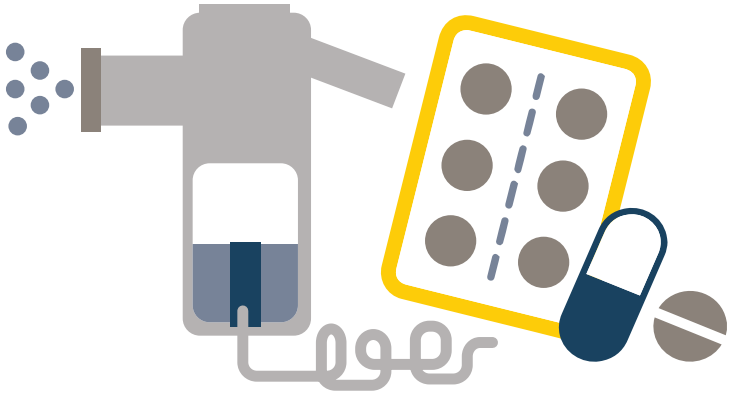


Antimicrobial treatments have been a key factor in the massive improvements in quality and length of life in people with CF over the last few decades. However, some CF infections are becoming resistant to the antimicrobial drugs that are used to treat them. Left untreated, these infections can cause permanent lung damage, meaning people are more breathless and have less energy to do day-to-day activities. Ultimately, a lack of effective antimicrobial drugs can shorten the lives of people with cystic fibrosis.

**"It's horrible being told you've developed a new bug, or 'superbug'.**

**"I'm now on a whole new drug regime, far tougher than any before. I take antibiotics each day that can make me feel exceptionally nauseous and I've had three gruelling hospital visits, both lasting four weeks, and yet despite this the resistant bug still lives inside me."**

**– Macauley, who has CF and developed one of these antimicrobial resistant infections**



## Precision medicines and CF lung infections

Cystic fibrosis is caused by inheriting two damaged copies of the CFTR gene, one copy inherited from each parent. Someone's CF 'genotype' is a description of which of these mutations they carry. In the last five years, a number of genotype-specific CF drugs, also known as 'precision medicines', have been developed. The latest of these, 'Kaftrio', is beneficial for the majority of people with cystic fibrosis.

As these drugs are so new, the effects of precision medicines on lung infections are uncertain. Early evidence suggests that while people may develop fewer new infections and have fewer exacerbations, they will still require treatment for more long-term, chronic infections.[4] This highlights the ongoing need to develop better, more effective ways to treat CF lung infections for those who benefit from precision medicines, in addition to the proportion of people for whom these drugs are not beneficial.

## The global challenge of antimicrobial resistance

Antimicrobial resistance refers to the way bacterial, viral and fungal infections have adapted to defend themselves against antimicrobial drugs, making the drugs ineffective. ('Antibiotic resistance' or 'antibacterial resistance', is a specific type of antimicrobial resistance, that refers only to bacterial infections where the bacteria have become resistant to the drugs.)

If an infection shows signs of being resistant to a first course of treatment, a different, stronger course of treatment is given. The second course of treatment is likely to have more unpleasant side effects. This iterative treatment continues until the infection is cleared, or a 'last resort' course of treatment has been tried and has also failed.

There have been no new types of antimicrobial drugs developed for over 30 years, and the world is running out of new effective treatments. This is partially due to the scientific challenges of antimicrobial discovery and development, as well as a lack of economic incentive.[5] Biopharmaceutical and biotechnology companies can be deterred from investing in new drugs because new drugs are used as a last resort (as the bugs haven't developed resistance to them) and there is a risk that the drug will not recoup the costs of its development.

There is increasing concern worldwide about antimicrobial resistance. The UK Government recently appointed the former Chief Medical Officer, Dame Sally Davies, as the Special Envoy on AMR to raise its profile in the G7 and G20. In 2019, the Government published its 5-year plan to tackle AMR[6] as further evidence of its commitment to this issue.

## Antimicrobial resistance in cystic fibrosis

While AMR is a concern for us all, people living with CF are particularly vulnerable to it. This is because antimicrobial drugs are an important part of day-to-day treatment for people with CF, as well as the specific challenges of treating CF-related lung infections.

In healthy lungs, there is a thin layer of mucus that helps the body move dirt and bacteria out of the lungs. The role of the healthy, functional CF protein is to keep the mucus thin; however, in people with CF, this mucus is much thicker. The thick, sticky mucus makes it harder to clear the lungs of infections and obstructs the airways, causing difficulty in breathing. Microbes adapt and thrive in the thick sticky mucus; it also obstructs the effective delivery of antimicrobial therapies to the lungs.

## How we are tackling the problem of AMR in cystic fibrosis

Since 2013, we've funded almost £8 million of research into understanding and treating lung infections. These projects are enhancing our ability to tackle AMR in CF, through development of new drugs, as well as investigating methods for earlier detection of infections and ways to increase the effectiveness of existing antimicrobial drugs.

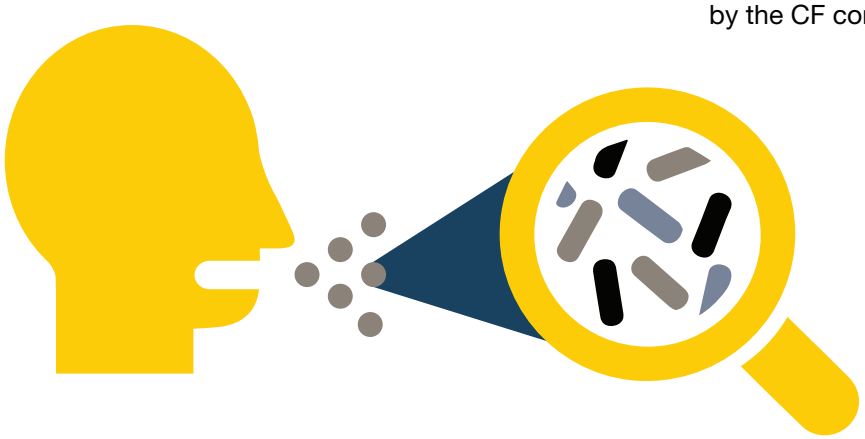
In this report, we have highlighted how scientific challenges of antimicrobial discovery and development and lack of economic incentive have created a shortage in new, effective antimicrobial drugs. The following areas of our activity demonstrate how we're working to overcome these challenges.

### Addressing the scientific challenges of antibiotic discovery

The UK Cystic Fibrosis Innovation Hub[7] is a ground-breaking strategic partnership between the Cystic Fibrosis Trust and the University of Cambridge that began in 2018. The focus of the Innovation Hub is on improving lung health.

Researchers within the Innovation Hub are tackling ambitious and innovative, high-risk programmes of work, where exceptional progress can be made rapidly. Part of this research addresses the scientific challenges of identifying new weak spots within bacteria for antibiotics to exploit, as well as pioneering techniques in drug design that haven't previously been applied in antibiotic drug discovery. One of the bacterial infections the researchers are focusing on is caused by the bacteria *Mycobacterium abscessus*.

*Mycobacterium abscessus (M. abscessus)* is a bacteria that causes an aggressive lung infection in people with CF and is extremely difficult to treat. It can take over a year of strong antibiotic treatments to clear, with damaging and unpleasant side effects, due to the bacteria's resistance to antibiotic treatments. Better treatments and eradication of this infection was highlighted as among the top 10 priorities for research by the CF community in 2017.[8]



To address this urgent need for more effective treatments for *M. abscessus* infection, researchers within the Innovation Hub are applying their genetics expertise to identify new weak spots within the bacteria, and are making good progress in designing new drugs that act on them.

A technique called fragment-based drug design (FBDD) is being used to design new antibiotics. It is a quicker and more efficient process than traditional methods of drug design.[9] Researchers within the Innovation Hub pioneered FBDD, resulting in new licenced treatments for cancer, and they are now applying it to design antibiotics to treat CF-related lung infections.

In June 2020, the researchers published some results[10] of their research so far, showing that they are making good progress in designing new antibiotics against *M. abscessus* infection. Their results demonstrate for the first time that FBDD is a technique that can be used to design new antibiotics.

Professor Andres Floto

**"There's a huge amount more work to do before these drugs are ready for testing in people, but they have the potential to one day treat multidrug resistant infections within the CF community and more widely around the world.**

**"Importantly, these ground-breaking results tell us that we can use the molecular structure of bacterial proteins to rationally design antibiotics, which could transform how we and others develop new antibiotics in the future."**

**– Professor Andres Floto, Principal Investigator of the UK CF Innovation Hub, University of Cambridge and Research Director of the Cambridge Centre for Lung Infection at the Royal Papworth Hospital**

**"I think the research they are doing is absolutely extraordinary. For me, a better treatment could have meant spending less time in hospital, having fewer side effects to the IV antibiotics and more time at home with the people I love."**

**– Mehro-Nissa, who has CF and was recently diagnosed with an *M. abscessus* infection**

By the end of the Innovation Hub funding, the aim is to have designed potential drugs ready to be tested as antibiotics in early stage clinical trials.

The Trust aims to raise £5 million over a five-year period for the Innovation Hub, which the University of Cambridge has committed to match pound for pound to £5 million. Co-investment with the University of Cambridge, and the leverage of these funds, has brought together a truly world-leading collaboration of exceptional calibre, including scientists who have been elected as Fellows of the Royal Society[11].

## Working together to address the barriers in CF antimicrobial drug translation

After new potential drugs have been discovered, there are still many more steps to complete before a drug can be licensed and used as a new antibiotic for CF lung infections – a phase of development known as 'translation'. These steps include lab-based 'preclinical' studies, testing the potential drugs in clinical trials and gathering the evidence for the medicines regulators to licence new drugs. Completing each step has specific requirements that can be time consuming and costly to meet.

Antimicrobial resistance is a challenging area for pharmaceutical companies to work in. The main reason for this is a lack of financial reimbursement strategies to ensure the company will recoup the costs of drug development. Cystic fibrosis antimicrobial drug discovery also represents its own challenges; for example, there is little guidance on how to conduct preclinical studies in this area and companies struggle to access patient samples, which are crucial for preclinical testing.

These challenges are recognised by Medicines Discovery Catapult (MDC), a government-funded not-for-profit organisation that is focused on reshaping the medicines discovery industry. The MDC Syndicate programme aims to provide an innovative model for patient-focused, collaborative drug discovery.[12]

Following discussions with people with CF and leaders in the field, the Cystic Fibrosis Trust and MDC launched the CF Syndicate in AMR in September 2019. The aim of the CF Syndicate in AMR is to get more antimicrobial drugs to people with CF faster, by bringing together a range of different experts from academia and industry plus people with CF to drive new research in the area. In the year since it was launched, the CF Syndicate in AMR has been gathering momentum to accelerate CF antimicrobial drug discovery. The steering committee has shaped a research agenda currently focussed on enabling access to CF samples, defining preclinical screening and testing pathways as well as activities that ensure that any drugs developed meet both clinical and patient need.

**"The Syndicate is about making the most of investments that the Trust has already made, accessing the innovative research that is taking place in small companies and also bringing on board people with CF, to make sure that we're focusing on their needs and priorities.**

**"We've bought a group of people together who wouldn't normally sit around a table together, including people with CF who are part of the steering committee. We've identified the key obstacles holding back CF antimicrobial drug discovery development and we're working collaboratively on ways to overcome them to enable the development of a pipeline of new CF antimicrobial drugs."**

**– Jessica Lee, Senior Programme Manager for the CF Syndicate in AMR, Medicines Discovery Catapult**


Jessica Lee

## Cystic fibrosis as an exemplar condition for tackling antimicrobial resistance

With recent access to life-changing, precision medicines, this is an exciting time for the CF community. However, people with CF will continue to need effective and safe antimicrobial treatments for lung infections. Due to AMR and the environment within the CF lung, this is becoming an increasingly difficult area of medicine, and one that is a priority area of research for the Cystic Fibrosis Trust. We hope our investments in research to tackle AMR and the ground-breaking approaches described in this report will be beneficial for people with CF in the future. Innovations made in tackling AMR in CF will also be applicable to solving AMR for all those with drug-resistant infections.

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