

New Drugs for Bad Bugs

The Innovative Medicines Initiative response to antimicrobial resistance

Antibiotic-resistant bacteria kill 25 000 people in the EU every year, and cost the economy €1.5 billion. The Innovative Medicines Initiative (IMI) programme New Drugs 4 Bad Bugs (ND4BB) represents an unprecedented partnership between industry, academia and biotech organisations to combat antibiotic resistance in Europe by tackling the scientific, regulatory, and business challenges that are hampering the development of new antibiotics. The programme currently comprises seven projects that are now starting to deliver on their promise of re-invigorating antibiotic research and development.

Antimicrobial resistance (AMR) is now widely recognised as a serious and growing threat to human and animal health worldwide. Meanwhile, new forms of resistance continue to arise and spread, leaving clinicians with few weapons to bring potentially life-threatening infections under control. Despite the recognised need for new antibiotics, the reality is that only two new classes of antibiotics have been brought to the market in the last three decades. The reasons for this are manifold.

On the scientific front, there is an urgent need for a greater understanding of how antibiotics work, how bacteria develop resistance to them, and what molecular mechanisms could be exploited to get round bacterial defence mechanisms.

Running clinical trials on new antibiotics is also both challenging and expensive due to regulatory requirements and the large numbers of patients required – put simply, a lot of patients have to be recruited to be sure of having enough patients with the resistant bacteria under investigation and to demonstrate that the new antibiotic is not inferior to comparable antibacterial drugs.

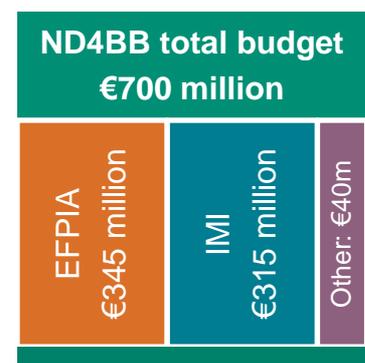
At the same time, because some antibiotics will only be used on a very small number of patients, the costs of development often exceed the potential return on investment. In other words, antibiotic development is simply no longer a financially viable option for pharmaceutical companies, and just a handful of pharmaceutical companies remain in the field.

The Innovative Medicines Initiative response

In its 2011 action plan on antimicrobial resistance, the European Commission called for ‘unprecedented collaborative research and development efforts to bring new antibiotics to patients’ by, among other things, launching an IMI programme in this vitally important area.

The result is New Drugs 4 Bad Bugs (ND4BB). The first projects kicked off in early 2013, and the programme now encompasses seven projects that are starting to deliver exciting results in diverse aspects of antibiotic development. Many projects focus on a group of bacteria called Gram-negative bacteria, which are notoriously tough to treat and are responsible for two thirds of the 25 000 deaths resulting from antimicrobial resistance reported in Europe annually.

The total budget of the programme now stands at around €700 million.



Getting drugs into bugs (and keeping them there)!

The **TRANSLOCATION** project focuses on identifying new ways of getting potential antibiotics into bacteria and preventing bacteria from destroying or expelling the drugs before they can take effect.

It is working primarily on Gram-negative pathogens such as *Escherichia coli* and *Klebsiella pneumoniae*; getting antibiotics into these bacteria is particularly challenging.

Key achievements

- Development of **new techniques** to analyse the uptake of antibiotics by bacteria.
- Worked out the **structure of 20 proteins** found in the membranes of bacteria that cause many infections. These proteins play a vital role transporting substances (including, potentially, antibiotics) into and out of bacterial cells.
- **Greater understanding** of the workings of efflux pumps (which bacteria use to expel antibiotics).
- Creation of a **database** to gather data from both new antibiotic research projects and abandoned ones.

Meet the projects

ND4BB programme overview
bit.ly/ND4BB

Research into the mechanisms of antimicrobial resistance

TRANSLOCATION
www.translocation.eu

Creating a platform for antibiotic development

ENABLE
nd4bb-enable.eu

Drug development & clinical trials

COMBACTE
COMBACTE-CARE
COMBACTE-MAGNET
All via: www.combacte.com

iABC
www.imi.europa.eu/content/iabc

Economics & stewardship

DRIVE-AB
drive-ab.eu

Building a drug discovery platform for antibiotics

The **ENABLE** project is creating and managing a drug discovery platform for testing and optimising molecules with the potential to become future drug candidates capable of treating infections due to resistant Gram-negative bacteria. Researchers with interesting early-stage programmes can apply to access the platform. Applications are assessed for their scientific potential; the project focuses its efforts on the programmes that are most likely to be successful. Universities and small companies selected to join the project have the opportunity to collaborate with experts in all areas of antibacterial drug discovery to help advance their molecule through the drug development process, through to clinical testing.

Key achievements

- Since the project started in February 2014, **50 anti-infective programmes** have applied to join the project to benefit from the platform.
- So far, **10 programmes** (7 from small biotechs) have been selected to join the project. Of these, **5 remain active**, having been identified as having the highest likelihood of succeeding in the clinic.
- There are **more programmes in the pipeline**. The project has a rolling open Call for proposals and the ENABLE team is continually reviewing submissions.
- The project has attracted the interest of **SMEs working on antibiotic development** both in Europe and beyond.

Establishing a pan-European network of clinical sites

The **COMBACTE** project is establishing a pan-European network of clinical trial sites that are ready to carry out high-quality clinical studies of new antibiotics for multi-drug resistant bacteria. The clinical site network (dubbed 'CLIN-Net') is supported by a network of laboratories ('LAB-Net') as well as networks comprising statistics experts working on innovative clinical study designs ('STAT-Net') and epidemiology researchers ('EPI-Net'). The hope is that these networks, which bring together vast amounts of expertise from universities, hospitals, the pharmaceutical industry, and more, will become the reference point in Europe for the clinical development of new antibiotics.

Key achievements

- The **CLIN-Net hospital network** includes **549 hospitals** in **344 cities** in **38 countries** in Europe. The project is now cataloguing these and, where necessary providing training to ensure all are qualified to run high quality clinical studies.
- The **LAB-Net** network counts **3-400 laboratories** in around **38 countries**.
- The network is actively involved in setting up and carrying out the **SAATELLITE study**, which is investigating a **drug called MEDI4893**. MEDI4893 targets a toxin produced by *Staphylococcus aureus*, a bacteria often associated with hospital-associated infections and linked to resistance issues. So far the SAATELLITE study covers **51 sites** in **8 countries**. Some **39 patients** have been enrolled so far.
- Another study that draws on the network is **ASPIRE**. ASPIRE aims to add to our **understanding of the incidence and causes of health-care associated infections (HAIs)** caused by two bugs: *S. aureus* and *Pseudomonas aeruginosa*. Patient recruitment started in June this year at a site in the Netherlands, and the project team is now busy adding further sites to the study.
- Plans for **further clinical studies** are being finalised.

Two further IMI projects launched in 2015 will build on the COMBACTE networks and use them to carry out research in specific areas.

COMBACTE-CARE focuses on infections caused by bacteria known as 'carbapenem-resistant enterobacteriaceae' (CRE). CRE are resistant to most available antibiotics and are so difficult to treat they are considered to be **one of the most dangerous drug-resistant bacteria in the world**. Worryingly, cases of CRE infections are on the rise in Europe and globally. COMBACTE-CARE aims to shed new light on the best ways to understand and treat CRE infections. It will also run clinical trials of a novel antibiotic combination product designed to tackle a sub-type of CRE infections for which there are limited or no treatment options. Further funding for the trial comes from the US-based Biomedical Advanced Research and Development Authority (BARDA); this will be used to support additional studies needed to advance the development of this urgently-needed treatment.

COMBACTE-MAGNET addresses the need for new approaches to preventing and treating **life-threatening infections among patients in intensive care units**. This group is particularly vulnerable to infections, for example in their lungs and airways. Increasingly, these infections are resistant to a range of antibiotics, leaving doctors with few options to treat their patients.

New treatments to help cystic fibrosis patients

Another project in the clinical development field is **iABC**, which started in 2015. Respiratory infections, frequently caused by drug-resistant bacteria, are the main cause of disease and death in people with **cystic fibrosis (CF) and bronchiectasis (BE)**. Thanks to inhaled antibiotics, patients now live longer than ever before and enjoy a better quality of life. However, infections are increasingly becoming resistant to the few drugs available, putting patients' lives at risk. The **iABC project** is advancing the development of **two inhaled antibiotics for patients with CF and BE**. It is also working to identify ways of improving clinical trials of treatments for these serious diseases.

New economic models for antibiotic development

The **DRIVE-AB project** got underway in autumn 2014. It focuses on the urgent need to develop a new business model for antibiotic development that will reinvigorate investments in this vital area while also addressing the issue of the responsible use of antibiotics. The project will have to tackle a contradiction at the heart of antibiotic development: on the one hand, pharmaceutical companies make money by selling large volumes of the drugs they develop. On the other hand, the use of new antibiotics should be restricted, so as to minimise the risk of bacteria developing resistance to them. As a result of this situation, sales are low and the costs of development often exceed the potential return on investment. This new project will develop concrete recommendations for new commercial models that provide industry with an incentive to invest in this area while ensuring that new antibiotics are used wisely.

Key achievements

- DRIVE-AB scientists discovered that a **30% drop in the efficacy** of antibiotics could result in **120 000 additional infections and 6 300 deaths per year** in the US alone among people who undergo common surgeries and chemotherapy treatments. The findings were published in the Lancet Infectious Diseases.
- The project is well represented in a new **series of papers** entitled 'Antimicrobials: sustainable access and effectiveness' that will be published by **The Lancet** on 18 November 2015.

About the Innovative Medicines Initiative

The Innovative Medicines Initiative (IMI) is working to **improve health by speeding up the development of, and patient access to, the next generation of medicines**, particularly in areas where there is an **unmet medical or social need**. It does this by facilitating **collaboration** between the key players involved in healthcare research, including universities, pharmaceutical companies, other companies active in healthcare research, small and medium-sized enterprises (SMEs), patient organisations, and medicines regulators. This approach has proven **highly successful**, and IMI projects are delivering **exciting results** that are helping to advance the development of urgently-needed new treatments in diverse areas.

IMI was launched in 2008 as a **public-private partnership (PPP)** between the **European Union**, represented by the European Commission, and the **European pharmaceutical industry**, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). The partnership was renewed in 2014 with the creation of the IMI 2 programme.

IMI currently has **around 70 ongoing projects**, with more in the pipeline. Some focus on **specific health issues** such as neurological conditions (Alzheimer's disease, schizophrenia, depression, chronic pain, and autism), infectious diseases (including antimicrobial resistance and Ebola), diabetes, lung disease, oncology, inflammation & infection, tuberculosis, and obesity.

Others focus on **broader challenges in drug development** like drug and vaccine safety, knowledge management, the sustainability of chemical drug production, the use of stem cells for drug discovery, drug behaviour in the body, and the creation of a European platform to discover novel medicines. IMI also supports **education and training** projects.

IMI finances

IMI has a budget of **over €5 billion** for the period 2008-2024. Half of this comes from the **EU's research and innovation programmes**.

The other half comes from large companies and organisations, mostly **EFPIA companies**. These do not receive any EU funding, but contribute to the projects **'in kind'**, for example by investing their researchers' time or providing access to research facilities or resources.

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