

IMI1 Final Project Report Public Summary

Project Acronym: COMBACTE-NET

Project Title: Combatting Bacterial Resistance
in Europe

Grant Agreement: 115523

Project Duration: 01/01/2013 – 30/11/2024

Executive summary

1.1. Project rationale and overall objectives of the project

The emergence of antibiotic-resistant bacteria (ARB) is a global problem, having recently been elevated to the top 3 threats identified by the World Health Organisation (WHO), and subject of numerous national and international government activities, including the Trans-Atlantic Task Force on Antimicrobial Resistance established by the US and EU presidencies. The estimated costs of ARB are around €1.5 billion per year in Europe, with an estimated 25,000 deaths (European Centre for Disease prevention and Control/European Medicines Agency “time to react”). While the threat of antimicrobial resistance is growing, so are the challenges to bringing forward new therapeutic options for patients infected with resistant organisms. There is a need for a better understanding of how antimicrobial resistance is evolving globally, of what novel molecular mechanisms can be exploited as new forms of antimicrobial therapy and of how to more efficiently develop new treatments so they can be more rapidly brought to patients in need. The overarching concept of IMI New Drugs for Bad Bugs (ND4BB) programme was to create an innovative public-private collaborative partnership that will positively impact all aspects of ARB through the discovery and development of novel agents for the treatment, prevention and management of patients with bacterial infections. COMBACTE-NET was one of the first projects to be launched under this programme with the aim of developing a broad European network of fully capable and Good Clinical Practice (GCP) compliant clinical investigation sites to execute clinical trials enabling the registration of novel agents to be used in the treatment of patients with bacterial infections. The growth and application of the network would be supported with robust microbiologic surveillance data and clinical epidemiologic data. To reduce the time and or cost of clinical development, novel clinical trial designs would be outlined and supported through analysis of publicly available and consortium-shared non-clinical and clinical data. In addition to executing the initial set of clinical trials, investigations of patient and pathogen-related biomarkers and the logistical and decision-making impact of rapid diagnostics would be conducted.

1.2. Overall deliverables of the project

The overall deliverables of the COMBACTE-NET Project are:

1. To establish a sustainable high-quality investigator network and surveillance programmes to support clinical development of new antibacterial agents
2. To increase the efficiency of antibiotic development through:
 - Analysing shared pre-clinical and clinical data sets and making recommendations for the development of novel antibiotic agents
 - Enhancing the application of Pharmacokinetics/Pharmacodynamics (PK/PD) to pre-clinical data to improve its ability to inform clinical study design
 - Utilising comparator data to inform novel clinical trial designs to reduce the burden on Phase 2 and Phase 3 trials, therefore making the development of antimicrobial products more feasible and efficient
3. To optimise application of rapid diagnostic tests in the context of clinical trials to better target patients for (early) inclusion in clinical trials

4. To explore potential biomarkers to enhance diagnostic and prognostic assessment of patients with bacterial infections
5. To increase the probability of success and efficiency of clinical development of suvratoxumab (a novel monoclonal antibody (mAb) for prevention of *S. aureus* infections) through
 - Evaluation of burden of disease and potential target population, utilising targeted active surveillance, followed by
 - Interventional Phase 1b/2 studies in the populations of interest, using study designs informed by the data collected from the epidemiologic surveillance studies
6. To establish population-specific surveillance programmes to support the clinical development of anti-*S. aureus* therapies
7. To conduct prospective clinical studies with novel trial designs to generate safety, pharmacology and proof of efficacy data for suvratoxumab
8. To assess *Clostridium difficile* Infections (CDI) incidence in patients ≥ 50 years of age treated with predefined antibiotic classes
9. To optimise the target population of the future Phase 3 DAV132 (a novel product which is designed to protect the intestinal microbiota from alterations, super-infections like CDI and side effects induced by a variety of antibiotics without impacting their bioavailability or systemic efficacy) randomised controlled trial (RCT)
10. To evaluate the efficacy and safety of DAV132 for the prevention of CDI in patients with newly diagnosed Acute Myeloid Leukemia or high-risk Myelodysplastic Syndrome and treated with intensive chemotherapy
11. To assess the effect of predefined antibiotic agents on the intestinal microbiota
12. To assess potential biomarkers predictive of CDI occurrence
13. To assess the safety, efficacy and PK of minocycline through the conduct of 2 phase 1 clinical trials
14. To quantify the health and economic consequence of deep joint infections due to *Staphylococcus aureus* after the primary hip and knee replacement
15. To obtain detailed insight in the feasibility and design of the ExPECMV Phase 3 vaccine trial in older adults and elderly.

1.3. Summary of progress versus plan since last period

Work Package	Planned achievements during last period	Missed planned objectives during last period
WP6D and E	To manage the site close-out of the SAATELLITE-2 Phase 2 study	Close-out visits were initiated in the total of 33 active sites. Of those, 23 sites were successfully closed, but at the end of the project (M143), there were still 10 that could not be completed.

1.4. Significant achievements since last report

Regarding grant management, In **WP1**, the Ecraid team was solely responsible for preparing the final report for COMBACTE-NET and liaising with the scientific and financial contacts at partners' institutions. Furthermore, the Ecraid team has also coordinated, written, reviewed and/or submitted the outstanding 10 project deliverables. The UMCU team has been working on the financial consolidation of the project and has liaised with the financial contacts at partners' institutions for the consolidation.

Additionally, the Ecraid Communications team in **WP1** has primarily worked on the conclusion of communication activities in COMBACTE-NET, as well as the transfer of information to ensure continuity and accessibility of e.g., scientific outputs – in particular on Ecraid's website after the domain of the COMBACTE website is no longer accessible. Communications was also responsible for updating the COMBACTE website and social media channels and sharing the final publications and updates from COMBACTE-NET.

In **WP2**, Ecraid's **CLIN-Net** has worked on presenting and organized follow-up meetings with the CLIN-Net hospital network to reflect on COMBACTE-NET, share lessons learned, and gather feedback from stakeholders, such as National Coordinators. Special attention has been paid on the continuity of work done in COMBACTE-NET and COMBACTE in Ecraid after the end of COMBACTE-NET project. WP1 and WP2 also participated in meetings (e.g., the meeting held in Limoges in June 2024, organized by CHUL, on the closure of WP6E and end of COMBACTE-NET).

In **WP6E and WP6D**, this last period aimed to proceed to the close-out visits of the sites participating in the SAATELLITE-2 trial. Activities were performed remotely by the CHUL clinical research associates in close collaboration with ARIDIS, the study sponsor. Of the 33 sites (11 located in France, 5 in Belgium, 8 in Spain, 4 in Israel, 1 in Greece, 3 in the Netherlands and 1 in Portugal), 23 were closed at the time of the project end.

1.5. Scientific and technical results/foregrounds of the project

Antimicrobial resistance (AMR) is a growing problem worldwide, and with few new drugs making it to the market, there is an urgent need for new medicines to treat resistant infections. Enter the IMI-funded COMBACTE project, which aimed to give antibiotic drug development a much-needed boost by pioneering new ways of designing and implementing efficient clinical trials for novel antibiotics. COMBACTE forms part of the New Drugs for Bad Bugs (ND4BB) initiative, IMI's wider programme to tackle AMR.

The COMBACTE projects formed public-private partnerships with the goal of addressing the challenges associated with developing antibacterial medicines capable of overcoming antibiotic resistance. The projects fell under IMI's ND4NBB, which consists of several projects that are finding solutions to the scientific, regulatory, and business challenges that are hampering the development of new antibiotics.

The focus of COMBACTE-NET was on establishing networks linking experts and research sites that could help to overcome the known challenges in the development of new antibiotics. Three crucial networks were set up – CLIN-Net, LAB-Net, and STAT-Net.

CLIN-Net (WP2) focused on connecting study sites, hospitals and primary care centres. This warm-based network lead to more successful contracting of study sites, more efficient regulatory approvals of studies, better site management and improved site selection for studies.

LAB-Net (WP3) connected laboratories to support the clinical studies. LAB-NET put in place good quality control systems for labs and dealt with the transport and analysis of samples as well as developing a biobank and repository based in Antwerp, Belgium.

CLIN-Net and LAB-Net worked together to engage over 1000 hospitals that are well trained for performing high-quality clinical studies with new antimicrobials. More than 1000 physicians and researchers were trained in good clinical practice and also 900 labs received trainings (e.g., Good Clinical Laboratory Practice trainings, External Quality Assessment panels) across 42 European countries.

Together, **both networks** contributed to the development of an efficient process for selecting the best sites for carrying out AMR drug trials. The CLIN-Net network in particular developed a portfolio of quality parameters that could be used to identify the most suitable sites. The process for picking a site to carry out an AMR study had to be well-defined, objective, transparent and justifiable, highlighting capacities and performance.

In total, 270 unique clinical sites in 26 countries were selected for 10 studies in COMBACTE-NET. When it comes to the number of times a site was selected, the total comes to 376. Out of this number, 71 sites participated in 2 or more studies in COMBACTE-NET.

In addition to the studies conducted in COMBACTE-NET, CLIN-Net and LAB-Net conducted all the observational and clinical trials within the COMBACTE projects and have also been involved in other studies, for instance in projects tackling COVID-19.

Overall, more than 47 000 patients were recruited as part of 47 studies, which resulted in 150 scientific papers examining eight different types of bacteria and viruses and ten infections. More than 100,000 specimens and 9,400 strains were collected for the repository and biobank.

STAT-Net (WP4) focused on innovative clinical trial methodology. A survey was held among pharmaceutical industry professionals to better understand the challenges and solutions for clinical development of new antibacterial agents ([Bettiol et al., 2015](#)). Based on that, the network of experts applied advanced pharmacological modelling to understand how to improve clinical trial design, as well as adding to global knowledge about optimal dosing ([De Velde et al., 2021](#)). Part of this work contributed to development of the new guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products. Another aspect of improving trial efficiency involved endpoint choice, therefore endpoints utilised in HAP/VAP trials were summarized, and a new hierarchical composite endpoint was developed based on expert input, ([Weiss et al., 2019](#)). It was assessed if – and how- historical data could be incorporated in novel trials to make them more efficient, evaluating the use of different types of priors. Multistate models were developed to better represent time-dependent clinical outcomes. This work was summarised in two white papers. In addition, trainings were created to teach the new generation of researchers about platform trials.

The network also developed a new shiny app ([Grodd et al., 2024](#)), that calculates the probability of an event of interest, like ventilator-associated pneumonia, occurring over time. This tool can be used to plan clinical trials on novel interventions against multi-drug resistant organisms and optimise sample size. It can also be useful for regulatory authorities to understand hidden effects in published randomised trials. For example, there may be a lot of early deaths that are overlooked if only judging the effectiveness of an intervention by looking at the overall reported effect estimates.

COMBACTE-NET **WP6A** included a two-staged epidemiology study intended to systematically assess the impact of patient related and contextual factors on the incidence of surgical site infections (SSI) and ICU pneumonia in the EU and to identify the patient subgroups that bear a disproportionate disease burden. Stage 1 was be a retrospective study analysing routinely collected surveillance data from hospital networks within the EU, while Stage 2 were two prospective cohort studies nested within routine prospective surveillance among surgical patients and/or ICU patients in sites identified during Stage 1. The study **ASPIRE-ICU** investigated *S. aureus* pneumonia in ICU patients and the study **ASPIRE-SSI** focused on *S. aureus* SSIs and postoperative bloodstream infections in surgical patients. WP6A delivered comprehensive epidemiological and genomic insights into *S. aureus* infections in European ICUs and surgical settings. Its findings contribute valuable evidence for infection risk stratification, prevention strategies, and future diagnostic innovation.

The key results of the ASPIRE-ICU:

- A predictive model identified *S. aureus* colonization at ICU admission as the strongest risk factor (OR 3.09).
- Neurological trauma increased risk (OR 1.61); recent antibiotic use reduced it (OR 0.56).
- Anti-alpha toxin antibody levels at baseline had no predictive value.
- Main results were published in the highly renowned JAMA Network Open ([Troeman et al., 2023](#)). Also, additional manuscripts were drafted based on the data and samples collected in this study.

The Key results for ASPIRE-SSI:

- Microbiome Study that included 16S rRNA sequencing of 256 respiratory samples. Also bioinformatics analysis aimed to understand microbiome dynamics in relation to pneumonia development.
- ASPIRE-SSI Study enrolled 5004 patients; 67.3% were *S. aureus* carriers.
- Carriers had a significantly higher infection incidence (2.55%) than non-carriers (0.52%).
- Independent risk factors were: Pre-op *S. aureus* colonization (aHR 4.38), Non-removable implants (aHR 2.00), Mastectomy (aHR 5.13) and neurosurgery (aHR 2.47), Higher BMI (aHR 1.05/unit increase). Population Genomics of ST398: 1079 ST398 genomes from human and animal sources across 25 countries were sequenced. Genome differentiation was mainly driven by geography ($R^2 = 0.18$), less so by biome ($R^2 = 0.04$) or time ($R^2 = 0.007$). Accessory genes were key in distinguishing human vs. animal strains.
- Laboratory and Diagnostic Insights: PCR test performance for *S. aureus* detection was submitted to *Journal of Molecular Diagnostics*. Central labs finalized microbiology and serum analyses. Data was shared in a central database for further analysis and publications

WP6B, the SAATELLITE Phase 2 trial, investigated the impact of suvatroxumab, a monoclonal antibody, which targets the alpha toxin of *S. aureus* that causes lung damage and eventually, VAP. This study represented a novel, randomised, double-blind, placebo-controlled, superiority design, utilising a primary clinical novel endpoint developed by COMBACTE, which was accepted by the EMA and FDA. This novel primary endpoint was a composite clinical endpoint: relative risk reduction of incidence of *S. aureus* pneumonia. It consisted of 3 components: 1) Clinical criteria, 2) Microbiological criteria, and 3) radiographic criteria. All 3 were required to be fulfilled concurrently for a study patient to be deemed having developed *S. aureus* pneumonia. The endpoint was adjudicated by a committee of HAP/VAP experts and radiologists who were blinded

to the patient's treatment assignment. This clinical endpoint was welcomed by the FDA and EMA because of the superiority design of the study. This endpoint was validated in the WP6B SAATELLITE study and was subsequently utilized by ARSANIS for their *S. aureus* mAb study, and the Phase 3 WP6E SAATELLITE-2 study.

The results of the SAATELLITE trial were an important milestone in COMBACTE-NET. It was the first interventional trial designed, initiated and completed within the COMBACTE consortium, demonstrating the success of the collaboration between the academic and industry partners in developing new drugs. It also provided the focus around which CLIN-NET and LAB-NET evolved.

Initially, **WP6C** included a phase Ib/2 study of suvratoxumab in prevention of *S. aureus* SSI. However, because of the lack of efficacy of suvratoxumab in preventing *S. aureus* SSI in animal models, decision to not pursue the development of suvratoxumab monotherapy in the SSI indication was taken in September 2014. AZ has looked into the development of a combo-antibody, an association of suvratoxumab and another monoclonal antibody that has already interesting results in pre-clinical studies, but AZ decided to no longer continue the development of suvratoxumab. It was therefore also decided to not start WP6C.

WP6D was represented in the overall support of communication and information dissemination of COMBACTE-Net PMO during the reporting period. Members of the WP6E study team were also part of the PMO and MB, ensured efficient collaboration with other WPs where needed.

During the period January 2023 – April 2024, only 1 clinical study continued within COMBACTE-NET **WP6E**, the **SAATELLITE-2** study, a Phase 3 Efficacy study of suvratoxumab for prevention of pneumonia caused by *S. aureus*. In this study, 50 sites were selected to enter the study. The protocol received approval in 8 countries (Belgium, France, Greece, Israel, Netherlands, Portugal, Spain and Switzerland). The study was put on administrative hold after a licensing dispute between Aridis and AstraZeneca on the 29th of March 2023. The study was put on hold while a solution to the dispute was sought. Before the study was put on hold, 33 sites were fully activated, of which 14 sites screened at least 1 patient. This resulted in 59 patients screened after obtaining informed consent, of which 24 patients were randomised and dosed. Thirty one (31) sites were fully trained with site initiation visits performed by the CRO. Online "Sample collection and management" (lab trainings) performed by LAB-Net in the early beginning of 2023 for 33 sites, in 8 countries; Belgium, France, the Netherlands, Israel, Spain, Greece, Portugal and Switzerland.

After exhausting multiple efforts to resolve the dispute and resume the SAATELLITE-2 study, a decision was made to terminate the study. During this period, amendment 15 was approved, resulting in a no-cost extension period of 7 months (new end date: 30th of November 2024) to allow for site closeout and study termination.

WP7 focused on studying *Clostridium difficile* infection (CDI) in hospitalized patients, assessing risk factors, prevention strategies, and novel interventions like DAV132. It consisted of two main studies: ANTICIPATE Study (Observational Study to assess the incidence of *Clostridium difficile* infections and to optimize conditions for an intervention study with DAV132) (WP7A) and DAV132 Clinical Trial (Preventing CDI in High-Risk Patients) (WP7B).

The **ANTICIPATE (WP7A)** study started in 2016, with the French biotechnology company Da Volterra as EFPIA partner. ANTICIPATE also aimed to support the development of DAV132, Da Volterra's

promising new therapeutic agent for the prevention of *Clostridium difficile* infections in high-risk patients. The results of this observational study have been published in two back-to-back publications in Nature Communication, in April 2021 ([Berkell et al., 2021](#) and [van Werkhoven et al., 2021](#)). A clinical paper (Incidence and predictive biomarkers of *Clostridioides difficile* infections in hospitalized patients receiving broad-spectrum antibiotics: a prospective cohort study) and a microbiota paper (Microbiota-based markers predictive of development of *Clostridioides difficile* infection).

In **WP7B**, a clinical study intended to assess the efficacy of DAV132 compared to placebo in preventing the occurrence of *C. difficile* infection in patients newly-diagnosed with an Acute Myeloid Leukemia (AML) or a high-risk Myelodysplastic Syndrome (MDS) treated with intensive chemotherapy, the site selection process was completed. Also regulatory approvals were obtained in 12/13 EU countries and 31/59 EU sites were initiated. Due to the bankruptcy of EFPIA partner DaVolterra, all planned activities related to the study were discontinued.

1. Observational studies

Several observational studies were carried out as part of COMBACTE-NET, to determine the incidence and the determinants of healthcare-associated infections, and all of the networks played a role. CLIN-Net and LAB-Net enabled the running of complex multinational studies across Europe as well as ensuring that appropriate training for observational studies was carried out. Complex data analysis could be carried out via STAT-Net, and the data that was collected was added to the EPI-Net repository developed by the COMBACTE-MAGNET project.

The COMBACTE-NET observational studies were: ASPIRE-ICU (WP6A) (understanding of *S. aureus* and *P. aeruginosa* infections in the ICU), ASPIRE-SSI (WP6A) (focusing on surgical site infection), ANTICIPATE (WP7A) (focusing on *Clostridioides difficile*), ARTHR-IS (WP9) (focusing on prosthetic site infections), EXPECT (WP10) (focusing on invasive extraintestinal pathogenic *Escherichia coli* (ExPEC) disease), and HONEST-PREPS (WP2-4; training ICUs for enrolling patients at risk for developing ventilator-associated pneumonia in clinical trials).

- i. **ASPIRE-ICU study (WP6A)** investigated the clinical course of patients that are intubated and receiving mechanical ventilation. Some of them carry *S.aureus* in their lungs at the time of intubation, without being infected. This can progress to infection, and ASPIRE-ICU sought to determine risk factors for these events. It was the biggest study of this kind ever carried out in the ICU, with 1933 patients. The robust data gathered from the ASPIRE-ICU trial helped to inform the clinical trials that followed.
- ii. **ASPIRE-SSI study (WP6A)** focused on *S. aureus* SSIs and postoperative bloodstream infections in surgical patients. The study enrolled 5004 patients, in 35 site in 10 countries across Europe.
- iii. **The EXPECT program (WP10)** took place in primary care (EXPECT-1) and in the emergency departments of several hospitals (EXPECT-2). In total, 4470 participants were enrolled in the EXPECT-1 study and 240 in EXPECT-2. The results of those studies were used to set up and conduct the Embrace study (which was not part of COMBACTE-NET), a global phase 3 study evaluating a new vaccine to prevent invasive *E. coli* infections.
- iv. **HONEST-PREPS** was an observational study involving 2165 ICU patients over 11 sites. The study gathered robust epidemiological data on ventilator-associated pneumonia (VAP) and trained ICUs across Europe on how to participate in a platform trial where patients that are at risk for or with VAP could be quickly enrolled. This project also provided the opportunity for cross-Atlantic collaboration with the US NIH-funded Antibiotic Resistance Leadership Group (ARLG) in expanding the fight against AMR. HONEST-PREPS has increased readiness of

clinical sites for participation in interventional studies, especially from widening countries, such as those in the Balkan region. A number of sites participating in HONEST-PREPS have now been integrated in the Perpetual Observational study on Ventilator-Associated Pneumonia (POS-VAP) which has been set-up as a warm-base network for RCTs within Ecraid. Data of HONEST-PREPS have also been used to inform simulations to validate the efficiency of different types of adaptive designs.

- v. The **ANTICIPATE (WP7A)** study started in 2016, with the French biotechnology company Da Volterra as EFPIA partner. It was an observational, epidemiological study involving hospitalized patients undergoing oral or intravenous broad-spectrum antibiotics treatments. The study aimed to determine the incidence of *Clostridium difficile* infections and to better prevent this severe pathology. It was being conducted in close collaboration with Da Volterra. ANTICIPATE also aimed to support the development of DAV132, Da Volterra's promising new therapeutic agent for the prevention of *Clostridium difficile* infections in high-risk patients.
- vi. **ARTHR-IS** was a retrospective multi-centre study which aimed to estimate the burden of SA-PJI after a hip or knee arthroplasty and their risk factors through a case-control design. Other objectives were to quantify the costs, number of hospitalizations, surgical procedures to treat and control the infection and finally the factors influencing therapeutic failure. The study selected 20 hospitals across 5 European countries in order to include 150 cases and 450 controls. This project was a collaborative initiative between the Hospital Virgen Macarena in Sevilla and GlaxoSmithKline as academic and EFPIA partners respectively. The results of this study provided critical information to develop strategies to prevent and treat SA-PJI and reduce treatment failures. Also the results from ARTHR-IS study helps in the design of future clinical trials to prevent SA-PJI prosthesis infection by providing reliable estimates on the incidence of SA-PJI and the subsequent burden on health care services.

2. Novel Interventional Studies:

- i. **The SAATELLITE Phase 2 trial (WP6B)** investigated the impact of suvrattoxumab, a monoclonal antibody, which targets the alpha toxin of *S. aureus* that causes lung damage and eventually, VAP. Instead of treating pneumonia, the study took an unprecedented route of enrolling patients colonised with *S. aureus*, using bed-side real-time molecular diagnostics, evaluating whether the monoclonal antibody could prevent the development of VAP. This study represented a novel, randomised, double-blind, placebo-controlled, superiority design, utilising a novel primary clinical endpoint developed by COMBACTE, which was accepted by the EMA and FDA (please see Section **WP6B, the SAATELLITE Phase 2 trial**, on p. 8 of this report for more information on this novel primary endpoint). This novel study design (including study endpoints) was published in a peer-reviewed journal (François B et al. Clin Infect Dis. 2016 Aug 15;63 Suppl 2:S46-51), and was subsequently utilised by two other studies for other molecules outside COMBACTE-NET (Arsanis *S. aureus* mAb study: clinicaltrials.gov NCT02940626; COMBACTE-MAGNET *Pseudomonas* mAb study: Chastre et al. Crit Care. 2022 Nov 15;26(1):355.) Seven hundred fifty seven (757) subjects were screened, and of those, 213 subjects were randomized to either the suvrattoxumab (n=111) or placebo group (n=102). The proportions with VAP at day 30 were 26% among placebo and 18 % among treated patients, yielding strong (though not statistically significant) signals of efficacy. However, the study contributed significantly to the further our understanding of the heterogeneity in ICU patients, and demonstrated further enhanced (statistically significant) efficacy in population under 65 years of age, and also demonstrated that such molecules may also provide pharmacoeconomic benefit by reducing the duration of stay of study subjects in the ICU and the hospital. The results of this landmark study were published in Lancet

Infectious Disease (François B, Jafri HS, Chastre J, et al. Lancet Infect Dis. 2021 Sep;21(9):1313-1323.)

- ii. **SAATELLITE-2 (WP6E):** In addition, the clinical trial infrastructure created in SAATELLITE (WP6B) programme, i.e., site selection-, study enrolment-, and endpoint adjudication committees, site engagement teams, study design including endpoints, all formed the basis for the EMA and FDA to agree to the subsequent suvatroxumab registrational **Phase 3 SAATELLITE-2 study (WP6E)**. The study was planned to be conducted across 200 global sites, In the initial stage, 75 sites in Europe were preselected, of which 50 were fully selected to participate in the study, and of those 33 sites were fully activated across Europe. Fifty-nine (59) patients were screened and of those, 24 patients were randomised and dosed in the study, when the study was placed on a non-safety-related, administrative hold due to a licensing dispute between AstraZeneca and study sponsor ARIDIS in March 2023. While the SAATELLITE-2 study was ultimately terminated in July 2024, the SAATELLITE programme created a legacy in establishing the benchmark for novel superiority design including new rigorous clinical endpoints acceptable to the regulatory agencies, and a successful public-private collaboration to develop novel investigational antimicrobial molecules to fight AMR.
- iii. **WP7B MICROCARE** was a clinical study intended to assess the efficacy of DAV132 compared to placebo in preventing the occurrence of *C. difficile* infection in patients newly-diagnosed with an Acute Myeloid Leukemia (AML) or a high-risk Myelodysplastic Syndrome (MDS) treated with intensive chemotherapy. Due to the bankruptcy of EFPIA partner DaVolterra all planned activities related to the study were discontinued.

The current limits of pivotal trials in clinical microbiome were described by [Vehreschild et al., 2023](#).

The results of COMBACTE-NET proved to be pivotal in helping us to better understand and treat the growing threat of antimicrobial resistance, now and in years to come. Overall, the COMBACTE projects, which are part of IMI's New Drugs for Bad Bugs program, have contributed to a wealth of new information in the fight against antimicrobial resistance.

1.6. Potential impact and main dissemination activities and exploitation of results

The project outputs of COMBACTE-NET were twofold. First, the **development of several novel investigational medicinal products (IMPs)** has been advanced. This includes studies on a monoclonal against *S. aureus*, a study to further support the development of a monoclonal against *P. aeruginosa* and a vaccine against *E. coli*. These drugs have all been brought closer to market with the studies performed in COMBACTE-NET.

Secondly, **a research infrastructure has been established**, that has become the operational European research institution [Ecraid \(European Clinical Research Alliance on Infectious Diseases\)](#). Ecraid, and before it CLIN-Net/LAB-Net, have by Q1 2025 contributed to the site selection and execution of 37 clinical trials. Some of these trials have led to the registration of novel medicines, or to establishing life-saving interventions in critically ill patients, most noticeably during the COVID-19 epidemic. Ecraid will continue to function as an independent not-for-profit research institution, aimed to facilitating both commercial and investigator-initiated clinical studies in Europe.

Ecraid is a pan-European single-access clinical research network for infectious disease. It is a 'warm base' network with the capacity and capability:

- To directly enroll patients with infectious diseases to generate evidence to support the testing and development of new diagnostic, preventive and/or therapeutic strategies and therapies;
- To conduct a broad range of rigorous clinical studies efficiently and rapidly;
- To function as a platform for a rapid research response in the face of serious infections and infectious outbreaks.

The project's scientific outputs contribute to the overall IMI objectives as follows:

- **Providing socio-economic benefits for European citizens** by the following:
 - a) **Reduced Healthcare Costs:** The predictive models allow for early identification of high-risk prosthetic joint infections caused by *Staphylococcus aureus* (SA-PJI) patients, enabling targeted preventive strategies and reducing the need for costly treatments, hospital readmissions, and prolonged hospital stays.
 - b) **Improved Patient Outcomes:** By minimizing the incidence of SA-PJI and associated complications, the project reduces the burden of long-term disability, such as loss of mobility, thereby enhancing patients' ability to participate in daily life and work.
 - c) **Evidence-Based Resource Management:** The detailed analysis of healthcare resource consumption provides data to inform efficient planning and allocation within European healthcare systems.
- **Contributing to the health of European citizens** by following means:
 - a) **Reduced Infection Rates:** The identification of pre- and perioperative risk factors supports the development of targeted prevention strategies, such as the development of new vaccines, optimized antibiotic prophylaxis and improved surgical practices, leading to fewer PJIs. Furthermore, the research completed in STAT-Net has significantly advanced the analysis of hospital infection data, aligning with IMI objectives by improving healthcare efficiency, reducing infections, and strengthening Europe's leadership in biopharmaceutical research.
 - b) **Enhanced Clinical Management:** The risk stratification tools facilitate personalized treatment plans, improving surgical and medical outcomes for patients with SA-PJI.
 - c) **Multidisciplinary Integration:** Although it was not one of the objectives, the results of the project reflect the importance of collaboration between orthopaedic surgeons, infectious disease specialists, and other healthcare professionals, ensuring comprehensive and effective management of PJI.
- **Increasing the competitiveness of Europe and help to establish Europe as the most attractive place for biopharmaceutical research and development** through:
 - a) **Innovation in Predictive Modelling:** The project's development of validated risk prediction models demonstrates Europe's capacity to apply advanced methodologies to complex clinical problems, fostering innovation in healthcare. Statistical innovations in COMBACTE-

NET support the biopharmaceutical sector in developing novel statistical methods to analyse data of new antimicrobial treatments and vaccines, reinforcing Europe's position as a global leader in health data analytics and medical research.

- b) **Platform for Future Research:** The project establishes a robust basis for clinical trials aimed at evaluating novel prevention and treatment strategies. In particular, the network established during COMBACTE has served as the basis of the [Ecraid Foundation](#), a one-stop-shop for high-quality research on infectious diseases. COMBACTE's hospital and laboratory networks, CLIN-Net and LAB-Net, represent the vital foundation on which COMBACTE and non-COMBACTE clinical trials have been performed over the last 12 years. The continuation of these networks in the future will highly benefit society in the face of antimicrobial resistance, emerging infectious diseases and pandemics. Over the next few years, these networks will continue their work within Ecraid as it builds a sustainable and joint European movement against infectious diseases. Ecraid is operational since January 2022 and is focused on efficiently generating rigorous evidence to improve the diagnosis, prevention and treatment of infections and to better respond to infectious disease threats. As such, Ecraid brings together clinical research in emerging infectious diseases with antimicrobial resistance. By focusing on collaboration between researchers and targeting current ethical, administrative, regulatory and logistical challenges, Ecraid facilitates clinical trials that can be done much faster, more efficiently and therefore at a lower cost. The ultimate goal is to have ongoing platform trials for major diseases and symptoms in Europe.

The challenges posed by emerging infectious diseases and antimicrobial resistance can only be effectively resolved through international collaboration and coordination. The COVID-19 pandemic has led to unprecedented public health measures across the globe. Meanwhile, the scientific research community has developed epidemiological intelligence, diagnostics, vaccines and antiviral treatments to reduce the impact of COVID-19. The expertise required to clinically evaluate new diagnostics, treatments, vaccines and other preventive and/or therapeutic interventions is not confined to a single institute or country. Collaboration and solidarity are key. COMBACTE-NET and the wider COMBACTE projects (COMBACTE-MAGNET, COMBACTE-CARE and COMBACTE-CDI) have already established a strong and important foundation, which will continue with the Ecraid Foundation, which has been one of the partners in COMBACTE-NET (and COMBACTE-CARE). The existing clinical and laboratory networks CLIN-Net and LAB-Net developed during the COMBACTE projects will now continue at the core of Ecraid, and will continue to expand and play an important role in the future.

Furthermore, the project outputs have the potential to be rapidly and broadly spread and taken up within the following groups:

- a) **Scientific Community:** 1. High-Impact Publications: Results have been published in high-impact journals, ensuring wide visibility among researchers. 2. Collaboration Opportunities: The project fosters partnerships for future studies, including those focused on innovative prevention and treatment strategies.

- b) **Healthcare Professionals:** 1. Clinical Implementation: The predictive models and risk factors identified are directly applicable to clinical practice, enabling healthcare providers to stratify patient risk and tailor interventions. 2. Training Programs: Workshops and educational materials disseminate findings, improving awareness and adoption among surgeons and infectious disease specialists.
- c) **Industrial Community:** Partnerships: Collaboration with industrial companies to integrate findings into new preventive strategies based on vaccines and monoclonal antibodies. Innovation Adoption: Predictive models and scoring systems can be incorporated into digital health platforms, enhancing decision-making in real-time.

Biopharmaceutical research in the EU/EEA a highly and ever increasingly regulated environment. On the plus side, this leads to high standards of patient safety and data integrity. However, the regulatory impositions on researchers have made studies more expensive and far more labour intensive. Besides regulatory issues, contract negotiations are a second major delaying factor in study initiation; these can easily take up to more than half a year.

In order to both remain competitive and compliant with the highest standards, academic researchers and private pharma companies require adequate and cost-effective support with the many administrative tasks in a trial, such as preparation of the study submission packages, safety reporting, and monitoring. The [Ecraid Foundation](#) now offers such services by its experienced staff to both academics and private companies, as a non-profit organization.

Furthermore, selection of optimal sites is a determining factor for the success of a clinical trial, as site recruitment performance determines whether a trial can be finished within projected timelines. The Ecraid Foundation, through its network is able to select the most appropriate clinical sites, based on aggregated data from earlier participation in studies and through its informal networks.

The project outputs also have the potential to contribute to the **Policy and Healthcare Systems:**

1. **Policy Development:** The project provides actionable data for developing infection prevention policies and guidelines at national and European levels.
2. **Scalability:** The methodologies and findings are adaptable to diverse healthcare settings, ensuring broad applicability across Europe.

In terms of **dissemination and adoption**, the findings from COMBACTE-NET are widely shared through:

- Publications in leading journals;
- Presentations at international conferences;
- Collaborations with hospitals and healthcare institutions;
- Open-source tools and practical guidelines.

1.7. Lessons learned and further opportunities for research

Synergies between public and private objectives were obtained by embedding academic research questions in clinical trials. This is particularly important in the difficult field of AMR. In this project, academics received access to large prospective patient cohorts and collections of patient samples, through studies that complied with the highest standards of data collection. The costs of such studies would have in many cases would have been prohibitive for purely academic research. On the other hand, private parties, through the collaboration, had access to high quality academic networks, and to early advice from key opinion leaders, based on the state-of-the art clinical practice. This could be achieved with competitive budgets.

The collaboration in this private-public partnership (PPP) has been essential in advancing the understanding and management of multidrug-resistant infections. Collaboration has been fundamental in several ways: funding, without which the project would not have been possible, with the collaboration of a large number of hospitals; the non-clinical vision, which allows for a different perspective on the research; and compliance with deadlines, which helps to complete the project.

As an example, the SAATELLITE study was essential in helping to build the COMBACTE network as the first efficacy trial initiated by the COMBACTE-NET consortium. This required a highly productive collaboration between academia and industry. SAATELLITE also greatly contributed to site capacity building through several investigator and laboratory trainings, site visits, site calls, providing sites with state-of-the-art molecular diagnostic tools and the opportunity for less experienced site personnel to visit top performing sites for on-site training.

The local coordinators of other studies in COMBACTE-NET also learned valuable lessons. As an illustration, the local coordinators involved in the EXPECT 1 study learned the importance of flexibility, innovative approaches and teamwork to ensure the continuation of research in a pandemic situation. To make an example, towards the end of February 2020, the first cases of community transmission of COVID-19 were confirmed in Italy and on 9 March 2020, the Italian government announced a national quarantine restricting the movement of persons and the closure of non-essential economic activities, with the result that recruitment in EXPECT 1 effectively came to a standstill.

The University of Verona (UNIVR), together with sponsors, General Practitioners (GPs), and the local ethics committee, adapted to social distancing by implementing remote consenting to continue their study despite disruptions. UNIVR coordinated the EXPECT studies in Italy, creating a network of GPs specialized in infectious disease research. EXPECT 1 helped establish strong collaboration with local health authorities and provided training on managing urinary tract infections. This collaboration involved 21 GPs and laid the groundwork for ongoing research partnerships in infectious diseases. Building on this success, the GP network recently joined the

EU-funded ECRAID-Base study on respiratory infections, showing enthusiasm for new multicentre research projects.

Recommendations for improving public-private partnerships (PPP)

The prime objectives of academic institutions are to answer research questions and to train young academics. For such studies, they need minimal assurances that projects will be seen through – i.e., financed – to the end. As an alternative, academic institutions may enter into PPP with purely commercial motives, generating revenue – without a specific research interest – in order to finance academic and research goals.

Private partners operate mostly in a free market, are fundamentally moved by financial drivers. Consideration at many levels may lead to decisions to temporarily halt or to permanently discontinue drug development projects. To successfully operate in a commercial environment, this flexibility is required. Also, a commercial partner may simply go bankrupt and not be able to fulfil its contractual obligations.

A successful PPP requires that both commercial and academic partners benefit from the collaboration. The synergies between commercial and research interests may be plentiful, but it is essential to on beforehand have a mutual understanding of what each party is to gain and which risks they are assuming. Contractual budgetary safeguards are to be in place.

Potential new research to further advance the field

It is becoming increasingly difficult for European academic institutions to run multicentre, multinational randomised clinical trials. Adequate project support is crucial in order to meet all logistical, training, legal and regulatory requirements. Setting up a research structure for just one single trial is expensive, and the dissolution of successful research collaborations after finishing a study or a project could be regarded as destruction of capital. It should be actively pursued to maintain such collaborations or networks actively involved in studies to maintain Europe competitiveness in running clinical studies in AMR.

A very specific way to optimize research utilisation, is through adaptive platform trials and perpetual trials, which may randomise over multiple interventions, simultaneously or consecutively, continuously striving to elucidate the optimal treatment strategy for a certain patient group. Research questions may be purely investigator-initiated, but their active status and possibility to rapidly start up a study and recruit participants, may make such studies attractive platforms for commercial parties to evaluate their new IMPs.

For patients acutely and severely ill due to infectious diseases, the standard randomised controlled trials may not be an adequate strategy to advance treatment strategies, as these tend to include non-representative patient groups and due to informed consent procedures are subject to delays. Approaches to tackle this problem include cluster randomised trials and delayed informed

consent, where patients are directly randomised to different accepted standards of care, providing consent for the use of their data at a later stage. Another strategy may be to set up research structures in which patients are pre-informed of possible RCTs that they might participate in, were certain medical situations to develop, and pre-sign informed consent for the studies they would wish to participate in.