

IMI New Drugs for Bad Bugs The COMBACTE-NET, COMBACTE- CARE, COMBACTE-MAGNET Consortium

MARC BONTEN

21 -22 JANUARY 2016



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UMC Utrecht

The typical phase III trial with a new antibiotic (through the eyes of a clinical physician)

- Design usually not really appreciated by clinicians/investigators (to rigid, not addressing the target population, to many exclusion criteria....)
- No/little direct interaction between the pharmaceutical company and investigators, most interaction through a global CRO CRA
- No/few possibilities to add (clinically relevant) substudies to main trial
- >80% of the initiated sites do not enroll a single patient
- Study takes ages (at least much longer than planned)
- Quality of data collection may be suboptimal



Innovative Medicines Initiative (IMI): a new way to collaborate

- ❖ The largest public-private partnership in life science R&D
- ❖ IMI1 Started in 2008, ended in 2014
 - 11 Calls launched



EFPIA = European Federation of Pharmaceutical Industries and Associations

Innovative Medicines Initiative (IMI): a new way of working

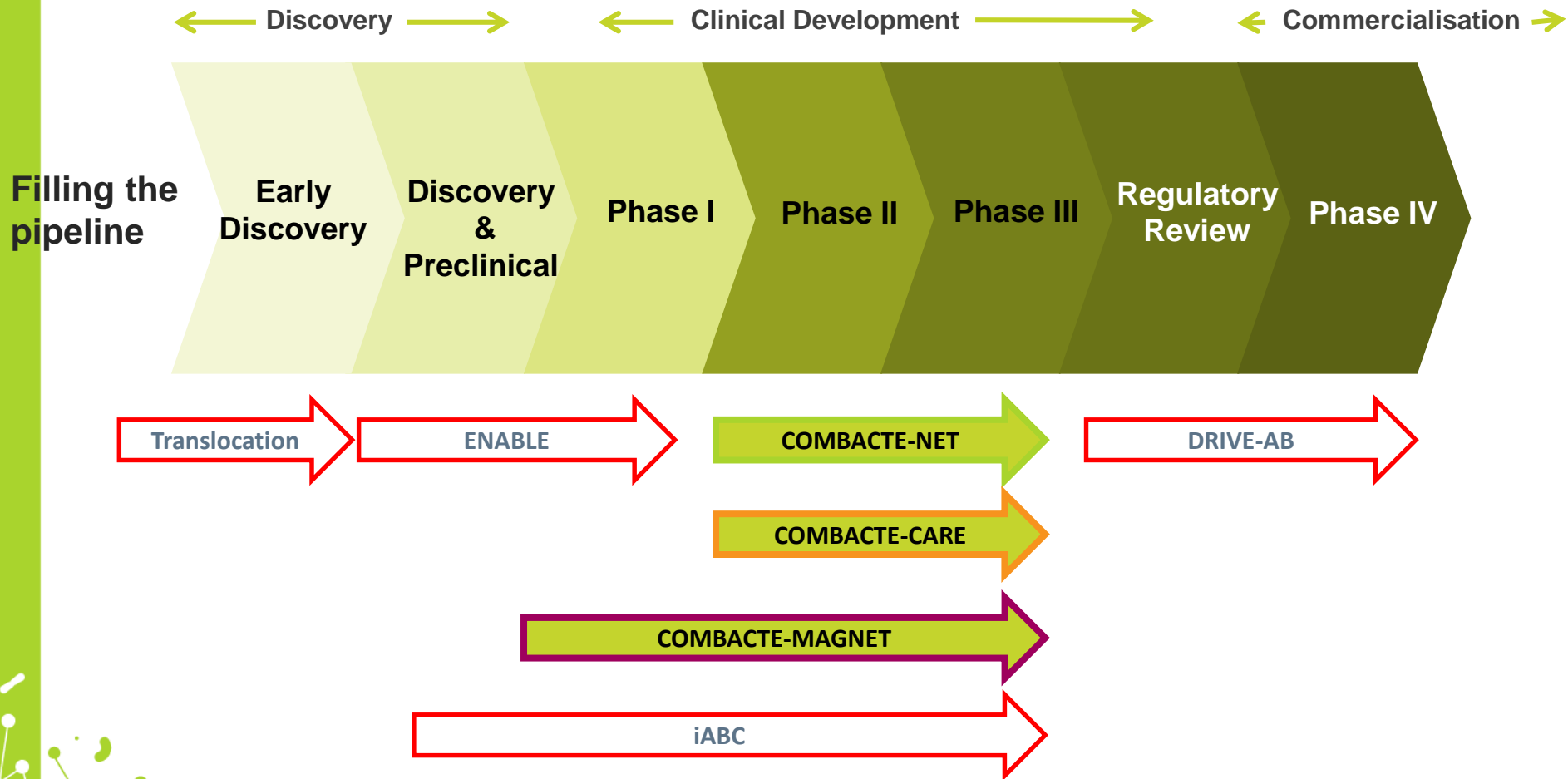
❖ Main objectives:

- Accelerating the development of safer and more effective medicines for patients in Europe
- *Boosting* the biopharmaceutical sector in Europe
- Create a collaborative environment for academia, industry, SMEs, regulators, patients

❖ **ND4BB** is part of the *Action plan against the increased threats from AMR* launched by the European Commission in November 2011

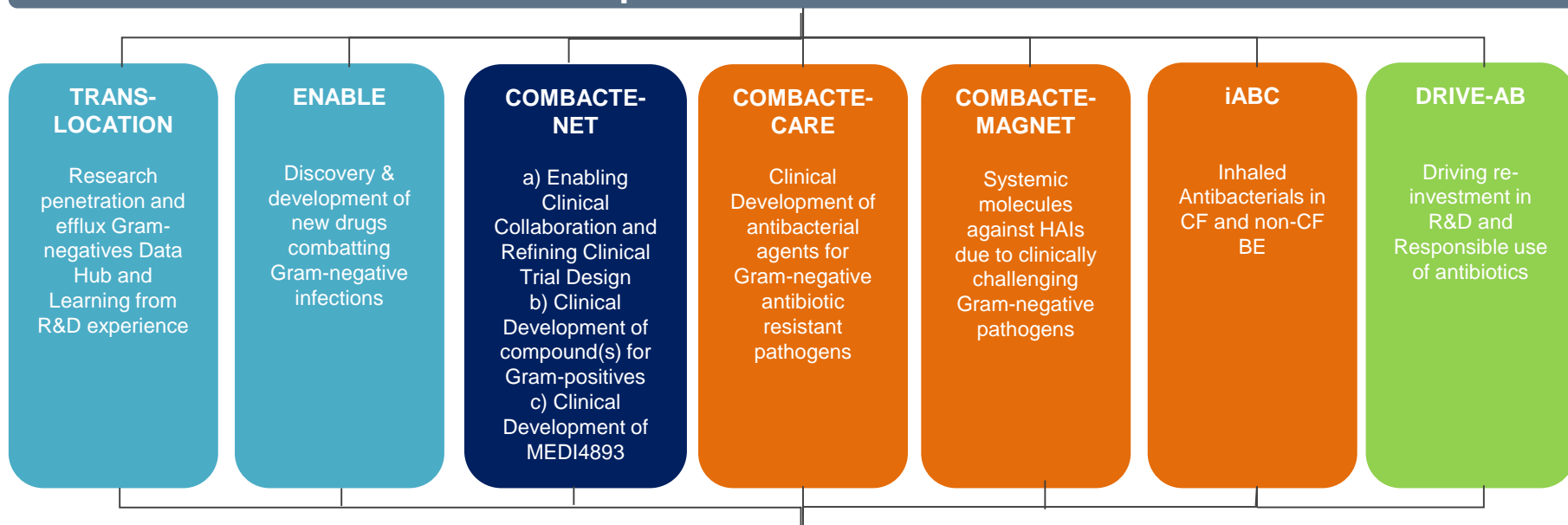


ND4BB Vision: Delivering a pipeline of new antibacterial agents to patients



Overall Architecture of the ND4BB Programme

ND4BB cross topic collaboration and dissemination



ND4BB Information Center

All data generated is submitted and is accessible to all consortium partners



Drug discovery



Drug development Gram-positives



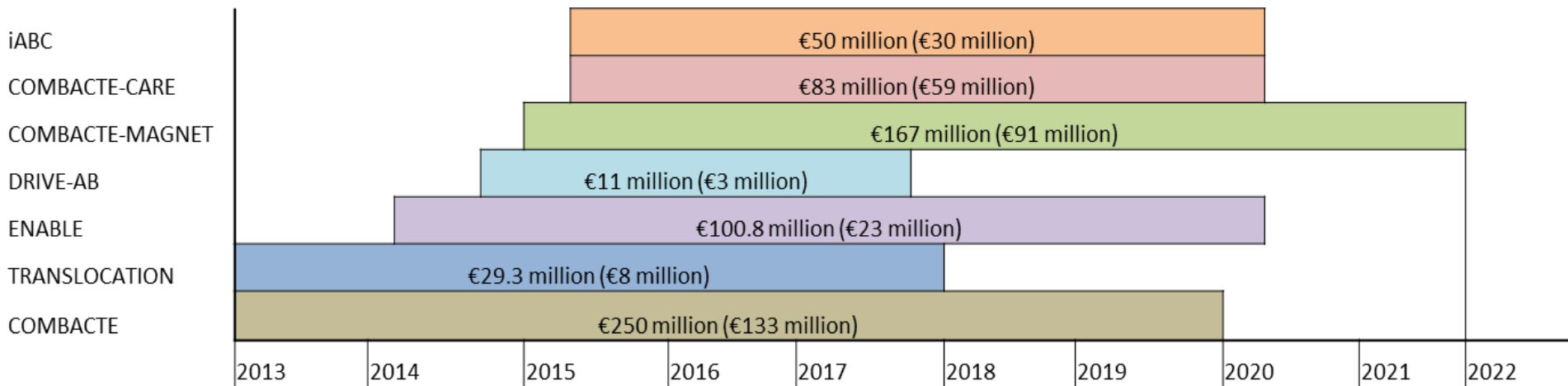
Drug development Gram-negatives



Economics and stewardship



Timeline and total budget estimation of the seven topics of the ND4BB programme (EFPIA contribution)



ND4BB-EFPIA Partners

COMBACTE-NET

• GSK, AZ-Medi, Da Volterra, Medicines Company, Janssen

COMBACTE-CARE

• AZ-Medi, GSK, Basilea

COMBACTE-MAGNET

• AZ-Medi, Aicuris, Basilea, GSK, Sanofi

TRANSLOCATION

• GSK, Sanofi, AZ-Medi, Basilea, Janssen

ENABLE

• GSK, Sanofi, AZ-Medi, Basilea

DRIVE-AB

• AZ-Medi, GSK, Astellas, Pfizer, Roche, Sanofi,

i-ABC

• Novartis, Basilea



Objectives

COMBACTE-NET/COMBACTE-CARE/COMBACTE-MAGNET

- ❖ **Create a self-sustaining antibacterial development network**
 - Expanding research and laboratory networks
 - Optimal alignment of clinical trials with investigator sites
 - Obtain clinical and epidemiological data

- ❖ **Increase efficiency of antimicrobial drug development**
 - Align clinical trials with cutting edge molecular methodologies and trial design
 - Deliver clinical trials with various candidate compounds from MedImmune/Astra Zeneca, Aicures, Astra Zeneca, Da Volterra, Medicines Company



The 4 pillars of the COMBACTE projects



CLIN-Net

High-quality clinical research network in all European countries with certification criteria and GCP Training program (lead: UMC Utrecht, M. Bonten)

LAB-Net

High-quality laboratory network in all European countries with assessment of existing laboratory methods, quality assessment system, specimens and strains repository (lead: U of Antwerp, H. Goossens)

STAT-Net

Network to improve clinical trials delivery, perform advanced biostatistical and PK/PD modelling studies, evaluate novel clinical design strategies using modern biostatistical concepts (lead: U of Geneva, S. Harbarth)

EPI-Net

Network to identify and map existing surveillance systems, to establish frameworks for data collection to support antibacterial drug development (lead: U of Tuebingen, E. Tacconelli)

All Academic & EFPIA partners



COMBACTE-NET

- 12 countries
- 30 academic partners
- 5 EFPIA partners

COMBACTE-MAGNET

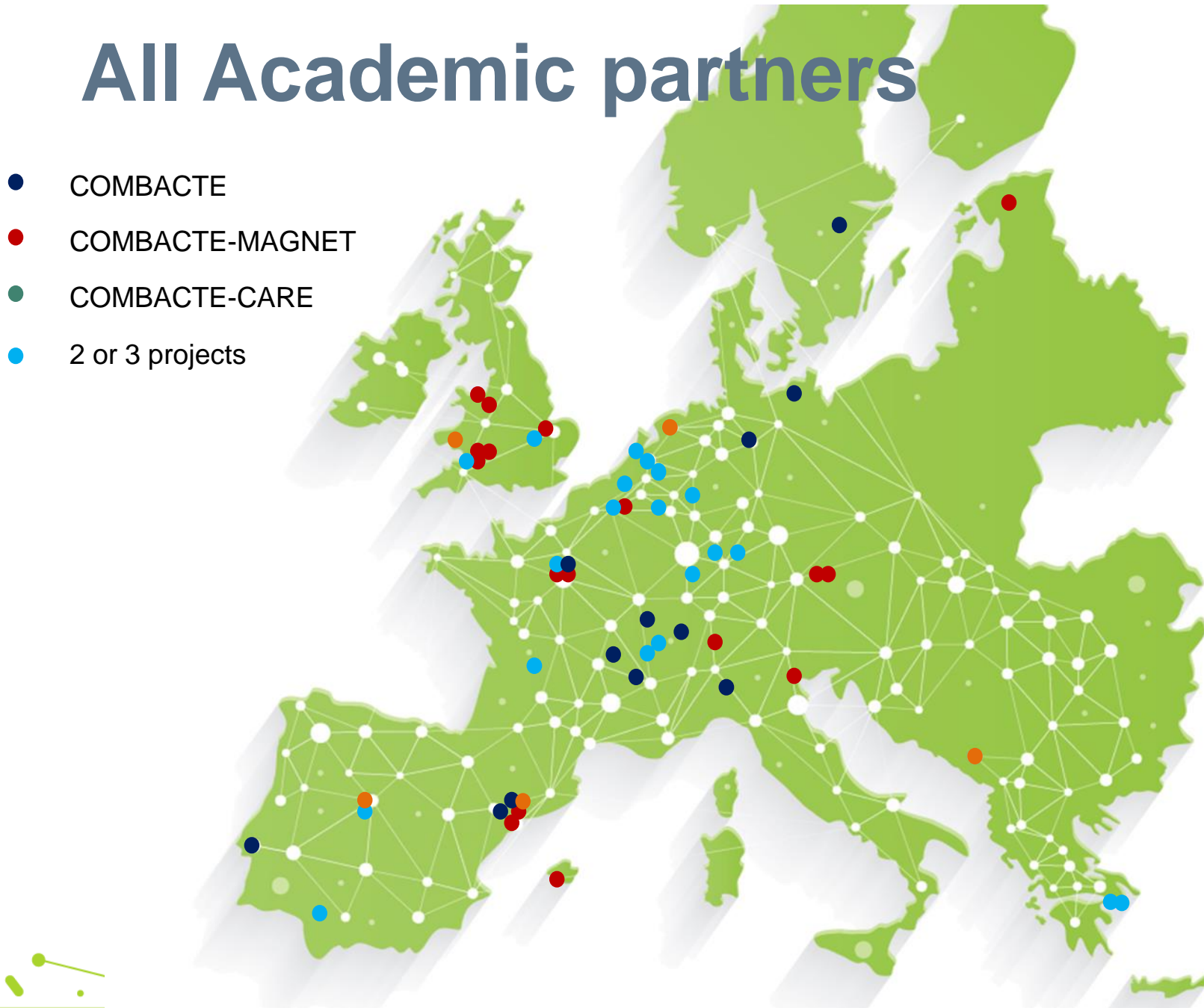
- 10 countries
- 34 academic partners
- 5 EFPIA partners

COMBACTE-CARE

- 11 countries
- 18 academic partners
- 3 EFPIA partners

All Academic partners

- COMBACTE
- COMBACTE-MAGNET
- COMBACTE-CARE
- 2 or 3 projects



CLIN-Net & LAB-Net in numbers Jan 2016

39 countries

437 cities

697 hospitals

1310 hospital contacts

426 laboratories

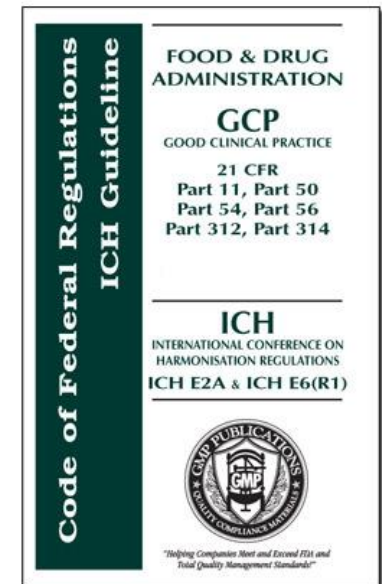
538 lab contacts



CLIN-Net GCP Course

Adequate execution of trials is essential in maintaining our network of investigators that can perform high quality clinical trials.

- ❖ **Helping member sites** in reaching and maintaining full GCP / ICH compliance.
- ❖ **Interactive:** Participants are challenged to compare GCP principles to their daily practice and discuss various cases with their fellow course participants, with UMCU moderators available for assistance.
- ❖ **Flexible:** The course can be paused and resumed during one month.
- ❖ Available since June 2014.
- ❖ In collaboration with European Forum for GCP (EFGCP).
- ❖ Compliant with **TransCelerate** and **PharmaTrain**.



Self-reported GCP Training status of Clinical Investigators in CLIN-Net

Year of completion training	% of investigators
2014-2015	33.5
Before 2014	16.4
Unknown	1.6
Not GCP trained	52.0



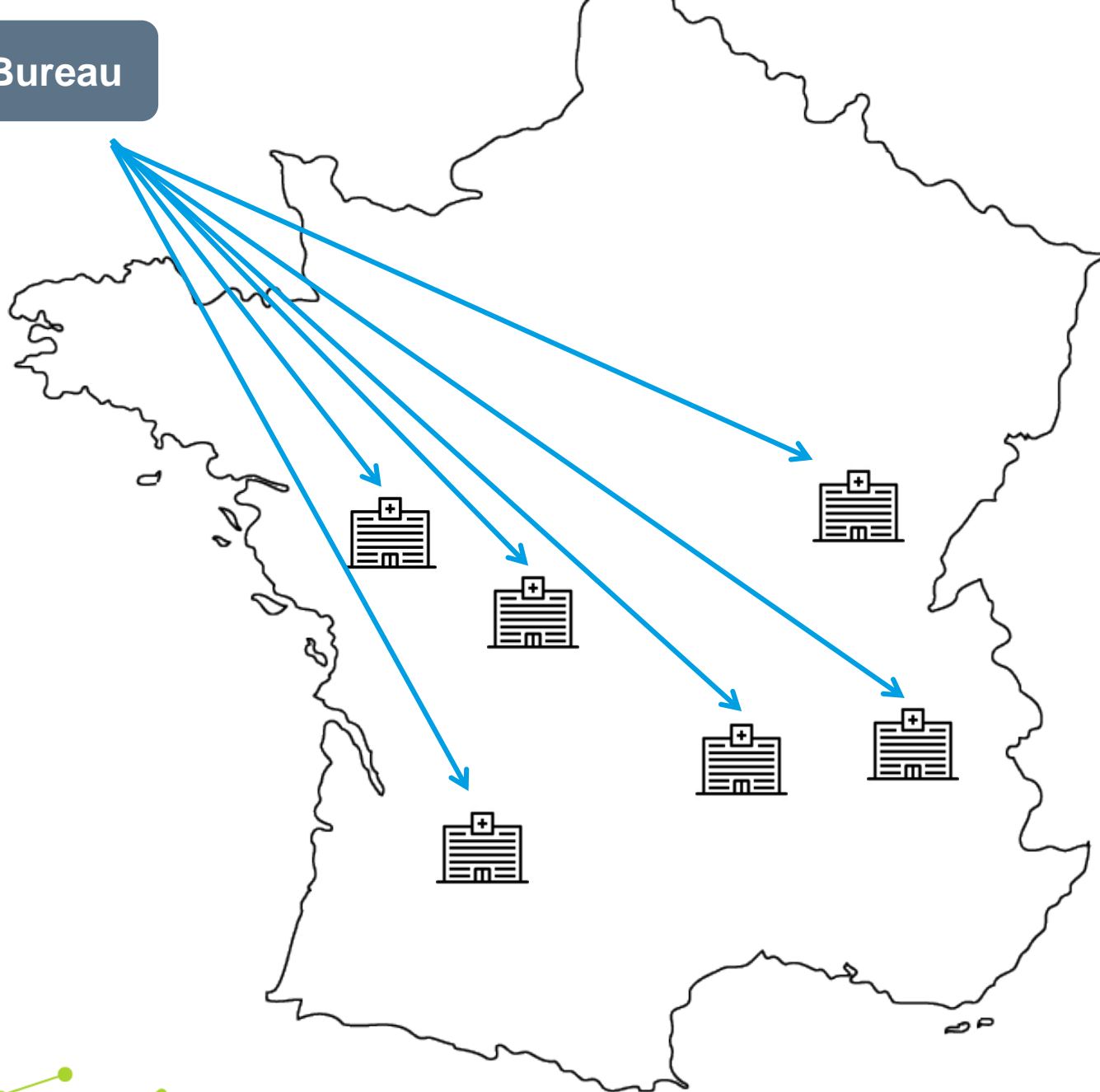
Investigators trained by CLIN-Net

Year	Online GCP course	Face to face GCP courses
2014	38	22
2015	96	55
Total	134	77

What does a network look like?

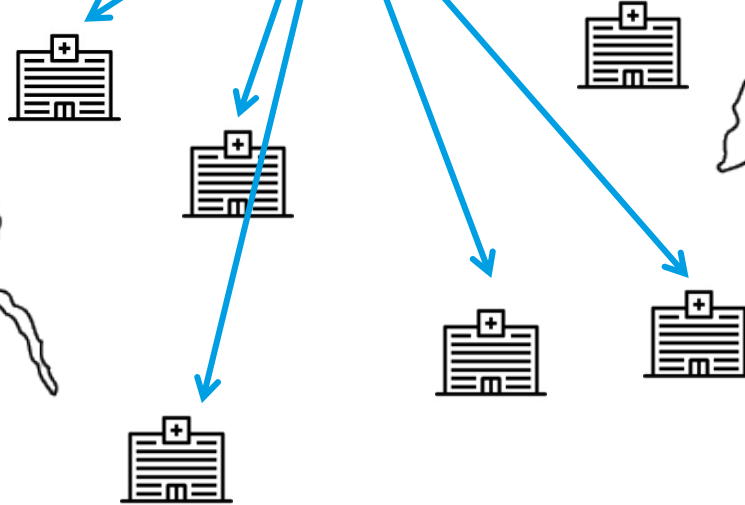


CLIN-Net Bureau

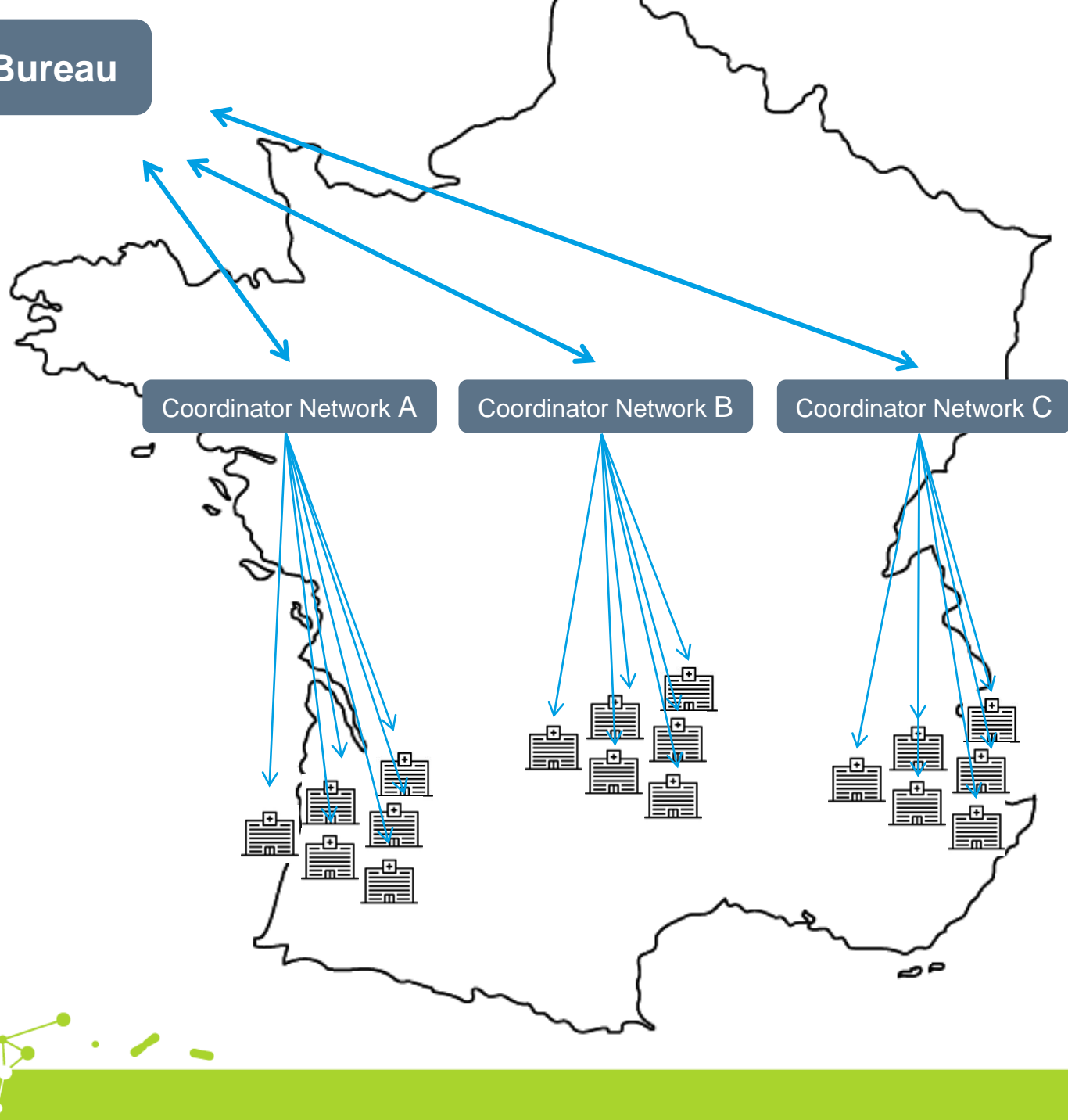


CLIN-Net Bureau

Regional
Coordinator



CLIN-Net Bureau



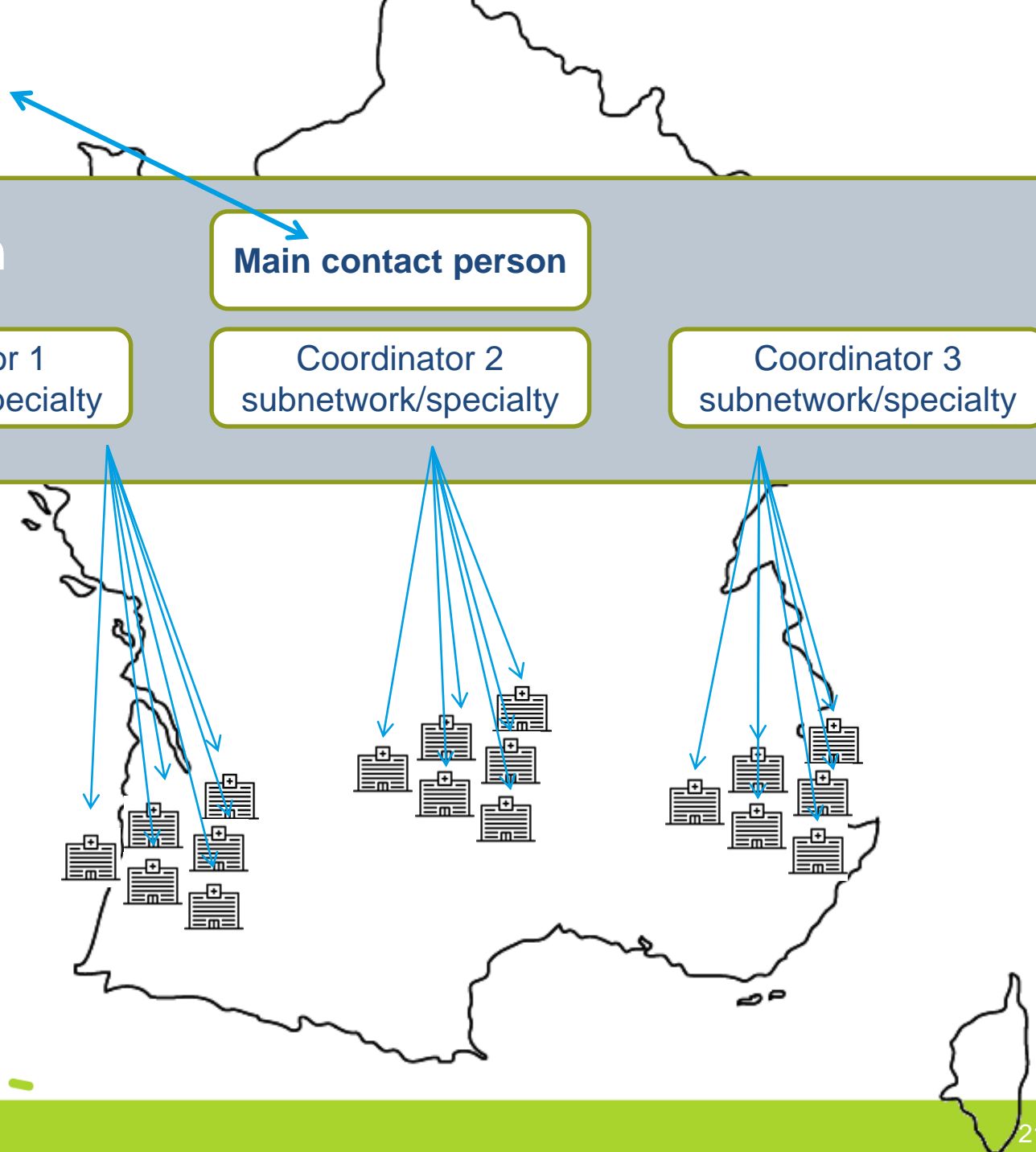
Regional team

Main contact person

Coordinator 1
subnetwork/specialty

Coordinator 2
subnetwork/specialty

Coordinator 3
subnetwork/specialty



CLIN-Net Bureau

LAB-Net Bureau

Regional team

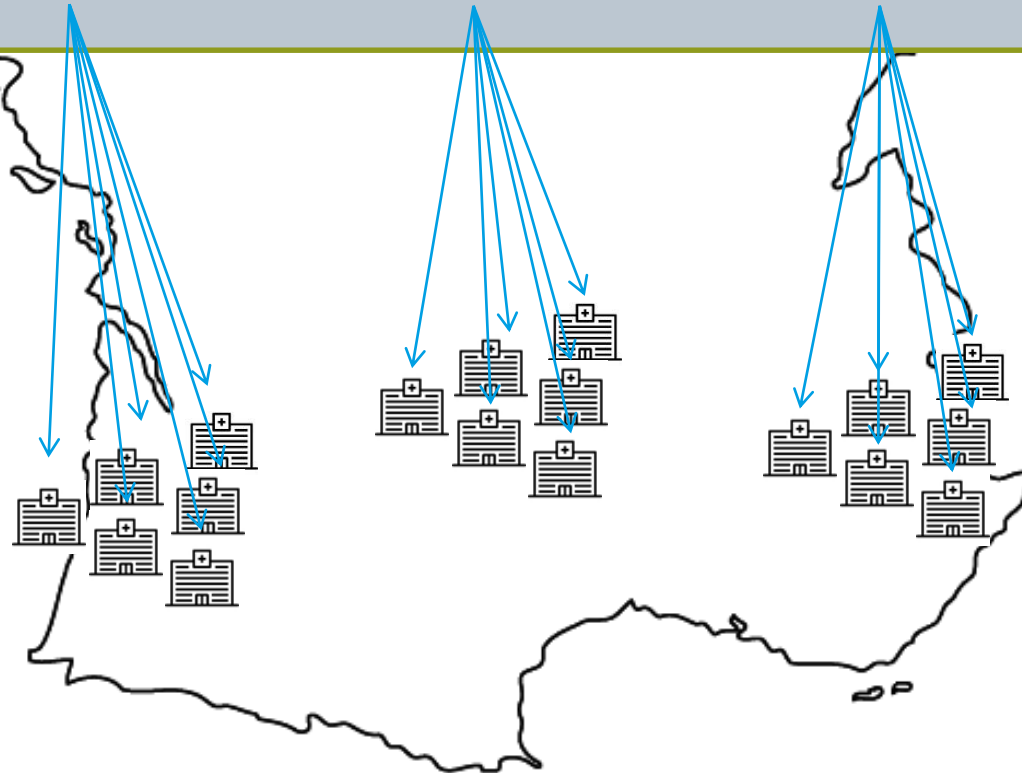
Main contact person

LAB-Net contact

Coordinator 1
subnetwork/specialty

Coordinator 2
subnetwork/specialty

Coordinator 3
subnetwork/specialty



Network Management System Feasibility Questionnaire Tool

- ❖ Research Online data management system, questionnaire tool
- ❖ Network Management System (NMS): COMBACTE Database
 - Contact information, trial experience, site facilities, epidemiology
 - Data from baseline- and trial feasibility questionnaires
 - Data from NMS can be updated by participants to ensure accurate information
- ❖ Optimizes site selection, facilitates communication with sites
 - Feasibility questionnaires prefilled from NMS / previous questionnaires
 - Search and selection tools for reporting and trials
- ❖ 1,500 questionnaires sent out, 900 have been completed
- ❖ Minimal work load for member sites is one of the key objectives



Ongoing studies

- SAATELLITE (AZ/MedImmune; Academic lead Bruno Francois, Limoges)
 - DB placebo-controlled phase II RCT; estimated sample size = 426
 - To evaluate in mechanically ventilated ICU patients
 - safety, tolerability, and pharmacokinetics of MEDI4893
 - effects of MEDI4893 on the incidence of *S. aureus* pneumonia
 - biomarkers associated with *S. aureus* disease severity and outcome
- ASPIRE-ICU (AZ/MedImmune; Academic lead Jan Kluytmans, Utrecht)
 - Observational study; estimated sample size = 2x2000
 - To determine
 - incidence of and risk factors for *S. aureus* and *P. aeruginosa* for ICU pneumonia
 - the role of antibodies against Gram-positive and Gram-negative bacterial virulence factors as biomarkers of disease risk and outcome
- EURECA (AZ; Academic lead Jesus Rodriguez Bano, Seville)
 - Observational study; estimated sample size = 800
 - To assess the clinical management and outcomes of patients with MDR-GNB infections

Ongoing studies

- REJUVENATE (AZ; Academic lead Oliver Corneli, Cologne)
 - Phase II PK-PD study with AZT-AVI (Aztreonam-Avibactam); estimated sample size = 40
 - Dose finding for global phase III study
 - Microdialysis substudy
- EVADE (AZ/MedImmune; Academic lead Jean Chastre, Paris)
 - DB placebo-controlled phase II RCT; estimated sample size = 492
 - To evaluate in mechanically ventilated ICU patients
 - safety, tolerability, and pharmacokinetics of MEDI3902, a bi-specific antibody
 - effects of MEDI3902 on the incidence of *P. aeruginosa* pneumonia
 - biomarkers associated with *P. aeruginosa* disease severity and outcome
- RESCUING (Aicuris; Academic lead Miguel Pujol, Barcelona)
 - retrospective study on UTI; estimated sample size = 1000
 - Estimating incidences for subsequent trials with antibiotic from Aicuris

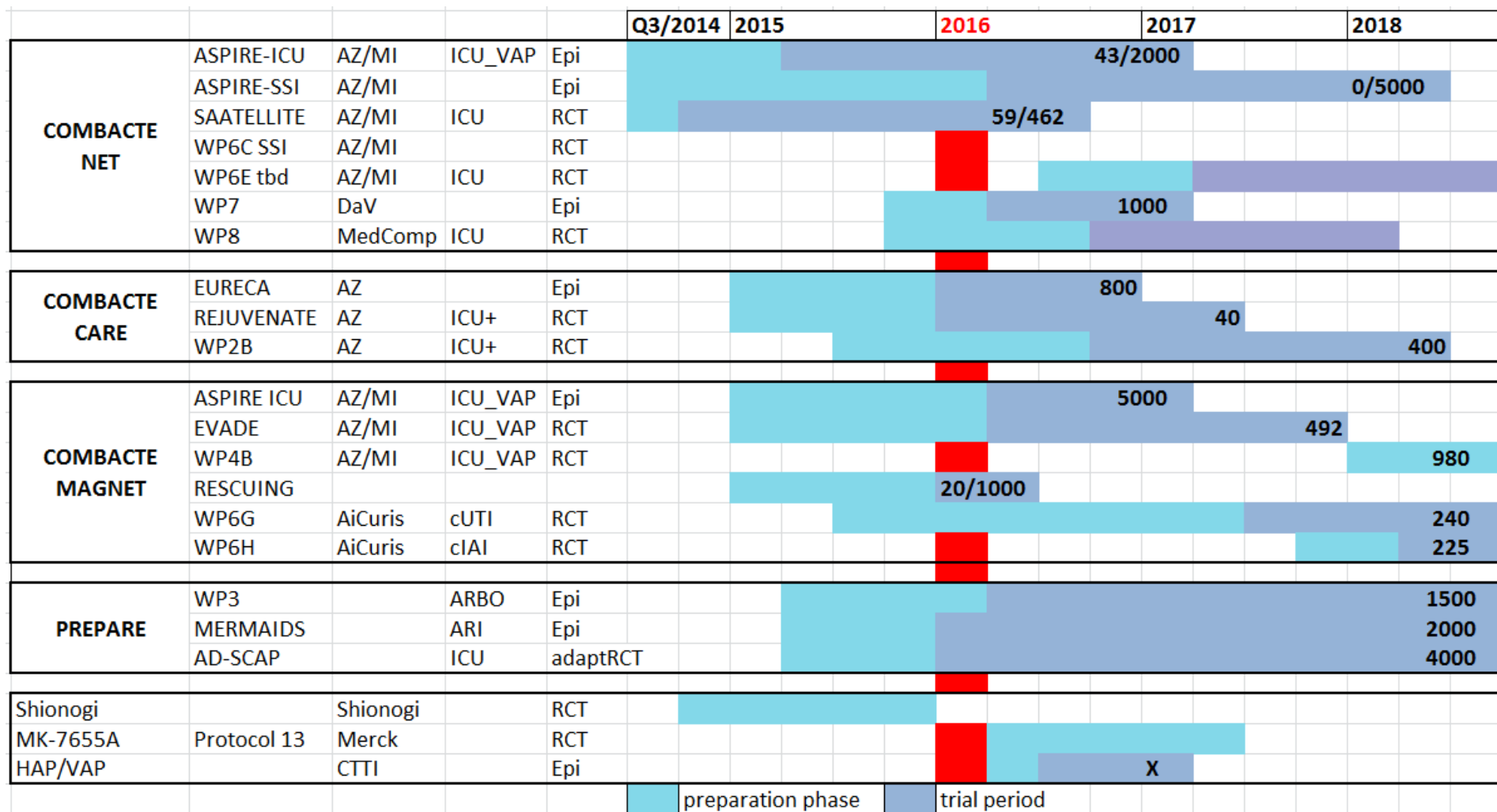


CLIN-Net & LAB-Net Study preparation and execution

Studies	Approached	Questionnaire completed	Selected	Initiated	Enrolling
COMBACTE-NET					
ASPIRE-ICU	159	40	17	6	3
SAATELLITE	156	94	91	60	17
COMBACTE-CARE					
EURECA	139	81	50	-	-
REJUVENATE	37	29	22	-	-
COMBACTE-MAGNET					
EVADE	198	113	52	-	-
RESCUING	48	31	21	21	3



The COMBACTE *pipeline*

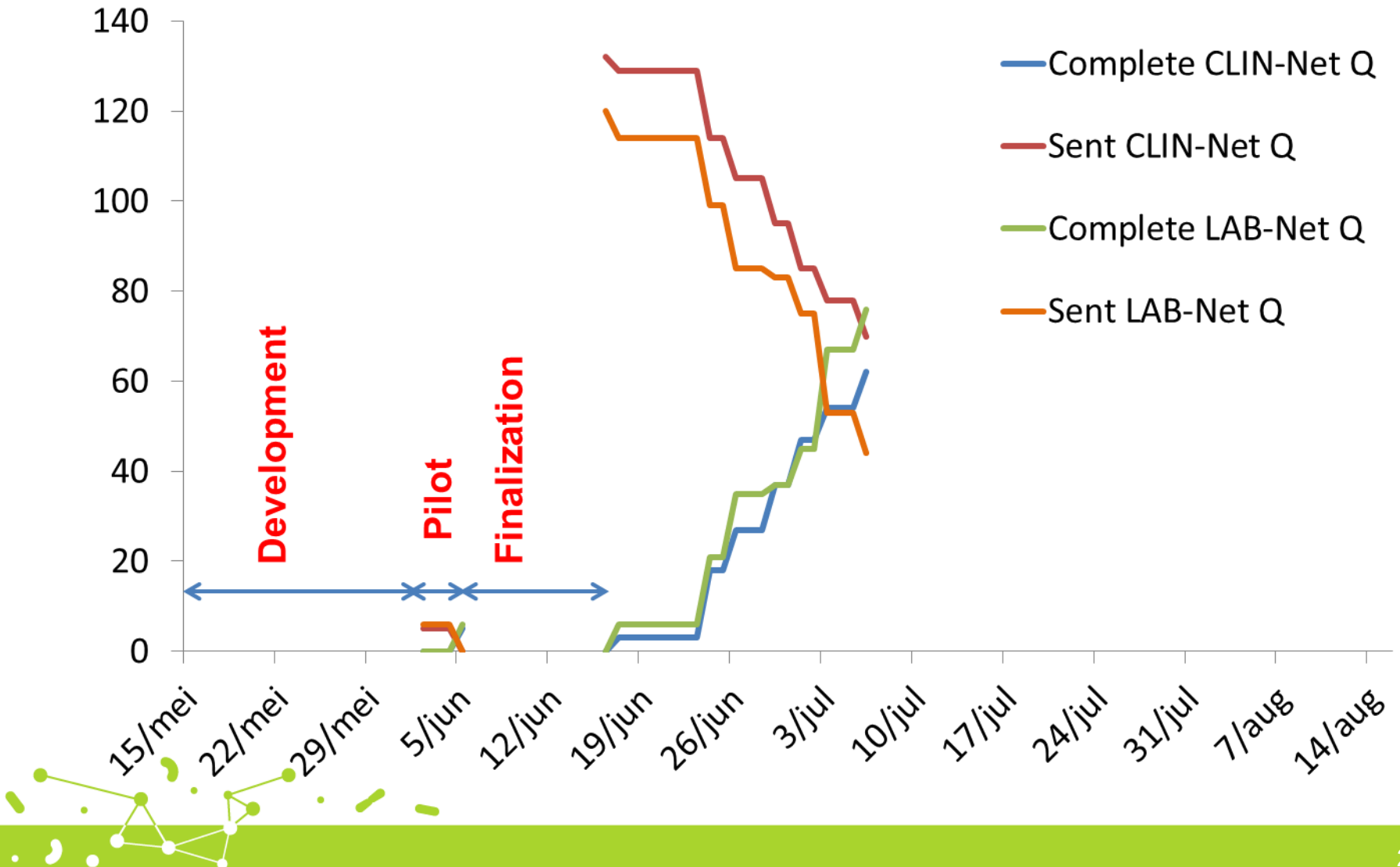


Shionogi study

- Multicenter, randomized, open-label clinical trial of a new siderophore cephalosporin or Best Available Therapy (includes combination of antibiotics) to treat severe infections caused by Carbapenem-resistant Gram-negative Pathogens.
- Type of infection: HAP/VAP, cUTI, sepsis/BSI
- 150 patients in EU & non-EU sites
- Question: Assistance in selecting 50 suitable clinical and laboratory sites in Europe



Shionogi study



COMBACTE Events



CLIN-Net & LAB-Net events

Presence at Medical Conferences	GCP / Lab Training	Investigator Meetings
ECCMID 2016- Amsterdam, Holland	LAB-Net detection of carbapenem-resistant Gram-negatives – Belgrade, Serbia, 2015	EURECA Investigator Meeting- Belgrade, Serbia
ECCMID 2015- Copenhagen, Denmark	GCP Training Face to Face- Madrid, Spain, 2015	COMBACTE Investigator Meeting- Copenhagen, Denmark
ECCMID 2014- Barcelona, Spain	GCP Training Face to Face, Belgrade Serbia, 2015	COMBACTE Investigator Meeting- Barcelona, Spain
ECCMID 2013- Berlin, Germany	LAB-Net workshop on Antibiotic resistance – Skopje, Macedonia, 2014	COMBACTE Investigator Meeting,- Berlin, Germany
SRLF 2016, - Paris, France	LAB-Net workshop on Antibiotic resistance – Pristina, Kosovo, 2014	REJUVENATE Investigator meeting- Cologne, Germany
CESAR 2015- Sibenik , Croatia	GCP Training Face to Face- Grindelwald, Switzerland, 2014	SAATELLITE Investigator Meeting- Vienna, Austria
DKOU 2015- Berlin, Germany		
Hungarian Society of Clinical Microbiology and Infectious Diseases 2015 - Szolnok, Hungary		
UKCCRF meeting-Cardiff, United Kingdom		
KNVM_NVVM 2014, Antwerpen, Belgium		
Hungarian Society of Clinical Microbiology and Infectious Diseases 2014 - Debrecen, Hungary		



WWW.COMBACTE.COM



ND/BB
COMBACTE

Combating Bacterial Resistance in Europe

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COMBACTE Photo Gallery

Latest news



COMBACTE Network Growing
The new COMBACTE NMS application has been used intensively in the last year... [Read more >](#)



STAT-Net meets with EMA Infectious Diseases Working Part...
Within COMBACTE, the STAT-Net group (WP4) aims to increase efficiency and success of randomized... [Read more >](#)



Study Update REJUVENATE
The REJUVENATE Face-2-Face Meeting was successfully held on 24 & 25 November in Cologne, ho... [Read more >](#)

All newsitems >

Latest Blog



Adressing Antibiotic Resistance Head-on
*Submitted by Cuong Vuong
Created on 12-14-2015*

Dear Colleagues, Several events and reports in the past weeks, months and years have had an important influence on the awareness of the global threat of antimicrobial resistance (AMR). There is now worldwide acceptance that antibiotic resistance is a threat that must be addressed urgently. The E... [Read more...](#)

About COMBACTE

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... [Read more](#)



Tackling Antimicrobial Resistance in Europe

Upcoming Events

January

25 CLIN-NET National Coordinator Meeting, Grindelwald, Switzerland
Duration: 6 hours (starts at: 10:00 hr)

March

08 COMBACTE Annual Meeting, Seville, Spain
Duration: 3 Days

Innovative Medicines Initiative and antibiotic resistance

Antibiotic resistance is broadly recognised as a growing global public-health burden.^{1,2,3} The effect of infections caused by multidrug resistant (MDR) bacteria, together with insufficient development of new antibiotics is a societal problem that needs a societal response—1 million deaths could occur as a result of MDR infections by 2025.⁴ With few new effective antibiotics in the pipeline, particularly against Gram-negative

microorganisms, this antibiotic armageddon could reach unprecedented proportions and imminent action is needed to address this public-health crisis. One of the major undertakings to address the challenges of developing new antibacterial therapies is the creation of public-private partnerships (PPPs), which are successful models for moving drug development forward in areas of unmet medical needs.



James King-Holmes/Science Photo Library

www.thelancet.com/infection Vol 15 December 2015

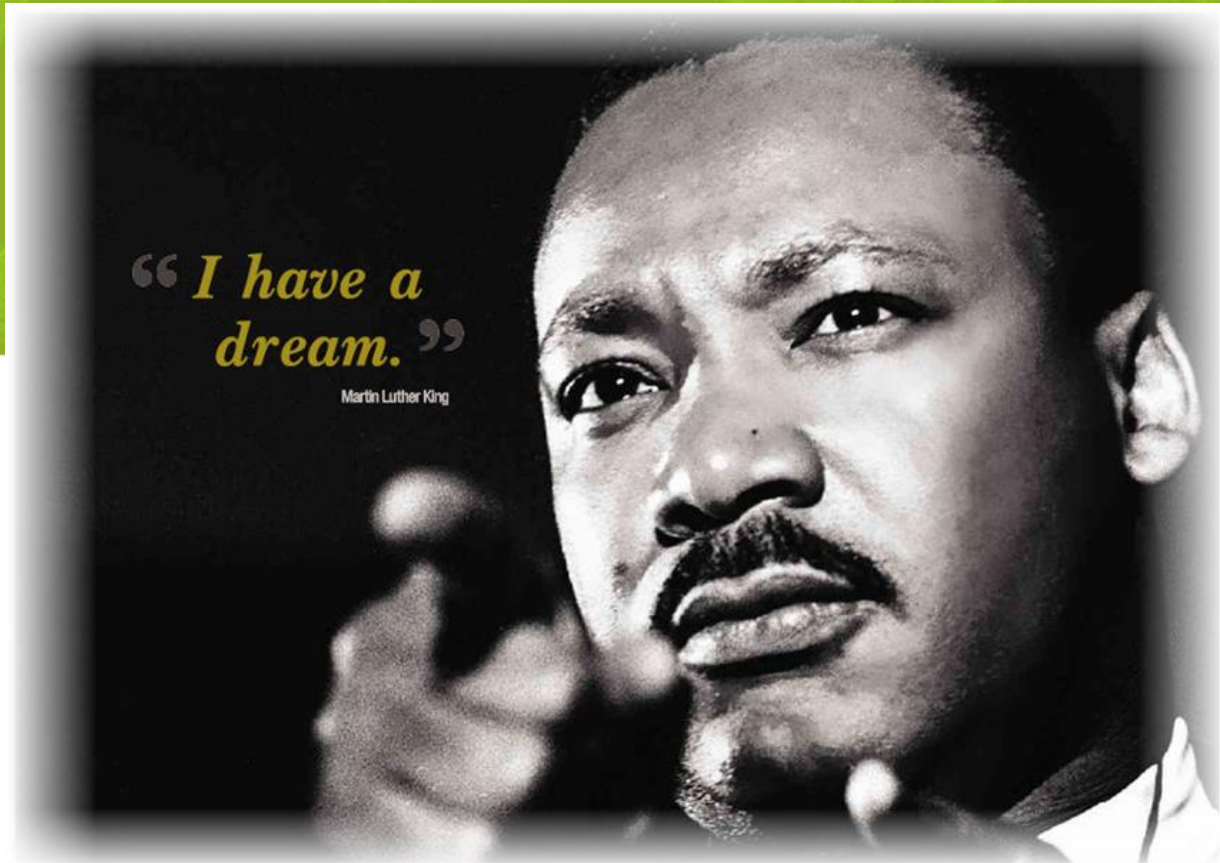
The Innovative Medicines Initiative's New Drugs for Bad Bugs programme: European public-private partnerships for the development of new strategies to tackle antibiotic resistance

T. Kostyanev¹, M. J. M. Bonten², S. O'Brien³, H. Steel⁴, S. Ross⁴, B. François⁵, E. Tacconelli⁶, M. Winterhalter⁷, R. A. Stavenger⁸, A. Karlén⁹, S. Harbarth¹⁰, J. Hackett¹¹, H. S. Jafri¹², C. Vuong¹³, A. MacGowan¹⁴, A. Witschi¹⁵, G. Angyalosi¹⁶, J. S. Elborn¹⁷, R. deWinter² and H. Goossens^{1,18*}

J Antimicrob Chemother 2016; **71**: 290–295



The future of CLIN-Net, LAB-Net, STAT-Net, EPI-Net



The future of CLIN-Net, LAB-Net, STAT-NeT, EPI-Net



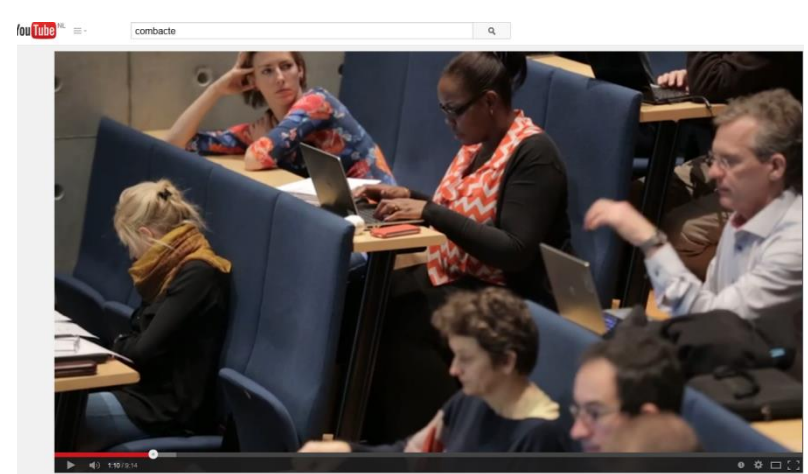
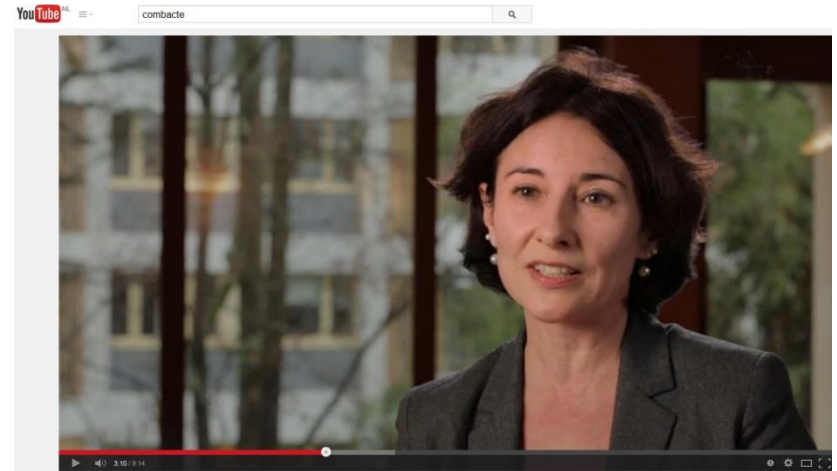
In 1962, Henri Tagnon founded the Groupe Européen de Chimiothérapie Anticancéreuse (GECA) with a group of European experts and visionaries aware of the importance of introducing a multidisciplinary approach and international cooperation in clinical research in Europe. In 1968, this successful initiative developed into the current **EORTC**.

Currently, the EORTC is both multinational and multidisciplinary and comprises over 300 hospitals and cancer centres in over 30 countries which include some 2,500 collaborators from all disciplines involved in cancer treatment and research.

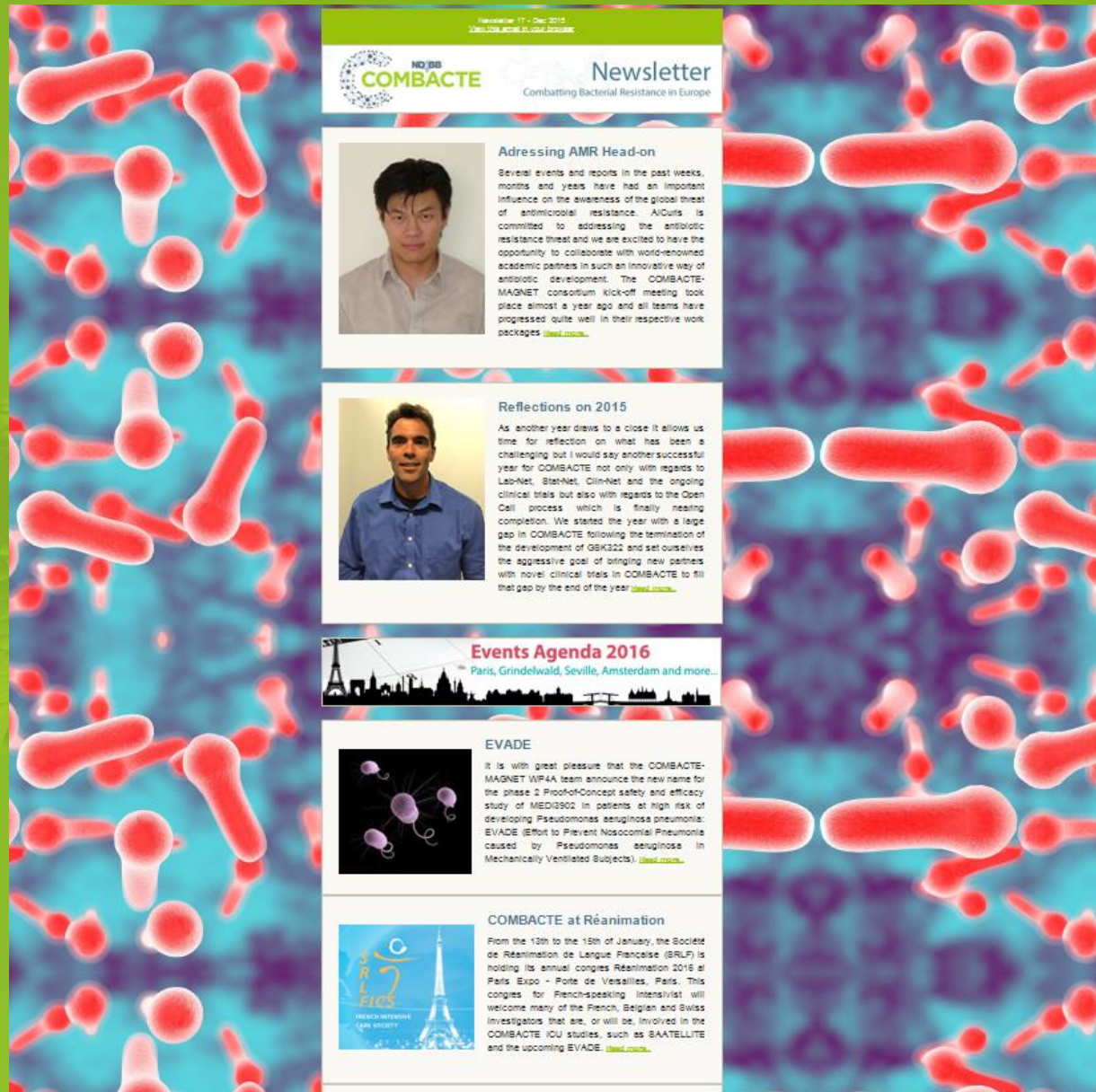
Presented on behalf of.....



Official COMBACTE video



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Newsletter 17 • Dec 2015
COMBACTE.NEWS@EU.COMBACTE

COMBACTE Newsletter
Combating Bacterial Resistance in Europe

Addressing AMR Head-on

Several events and reports in the past weeks, months and years have had an important influence on the awareness of the global threat of antimicrobial resistance. AQuora is committed to addressing the antibiotic resistance threat and we are excited to have the opportunity to collaborate with world-renowned academic partners in such an innovative way of antibiotic development. The COMBACTE-MAGNET consortium kick-off meeting took place almost a year ago and all teams have progressed quite well in their respective work packages [Read more...](#)

Reflections on 2015

As another year draws to a close it allows us time for reflection on what has been a challenging but I would say another successful year for COMBACTE not only with regards to Leo-Net, Stel-Net, Clin-Net and the ongoing clinical trials but also with regards to the Open Cell process which is finally nearing completion. We started the year with a large gap in COMBACTE following the termination of the development of GBK322 and set ourselves the aggressive goal of bringing new partners with novel clinical trials in COMBACTE to fill that gap by the end of the year [Read more...](#)

Events Agenda 2016
Paris, Grindelwald, Seville, Amsterdam and more...

EVADE

It is with great pleasure that the COMBACTE-MAGNET WP4A team announce the new name for the phase 2 Proof-of-Concept safety and efficacy study of MEDIQ502 in patients at high risk of developing Pseudomonas aeruginosa pneumonia: EVADE (Effort to Prevent Nosocomial Pneumonia caused by Pseudomonas aeruginosa in Mechanically Ventilated Subjects). [Read more...](#)

COMBACTE at Réanimation

From the 13th to the 15th of January, the Société de Réanimation de Langue Française (SRLF) is holding its annual congress Réanimation 2016 at Paris Expo - Porte de Versailles, Paris. This congress for French-speaking intensivists will welcome many of the French, Belgian and Swiss Investigators that are, or will be, involved in the COMBACTE ICU studies, such as SAATELLITE and the upcoming EVADE. [Read more...](#)

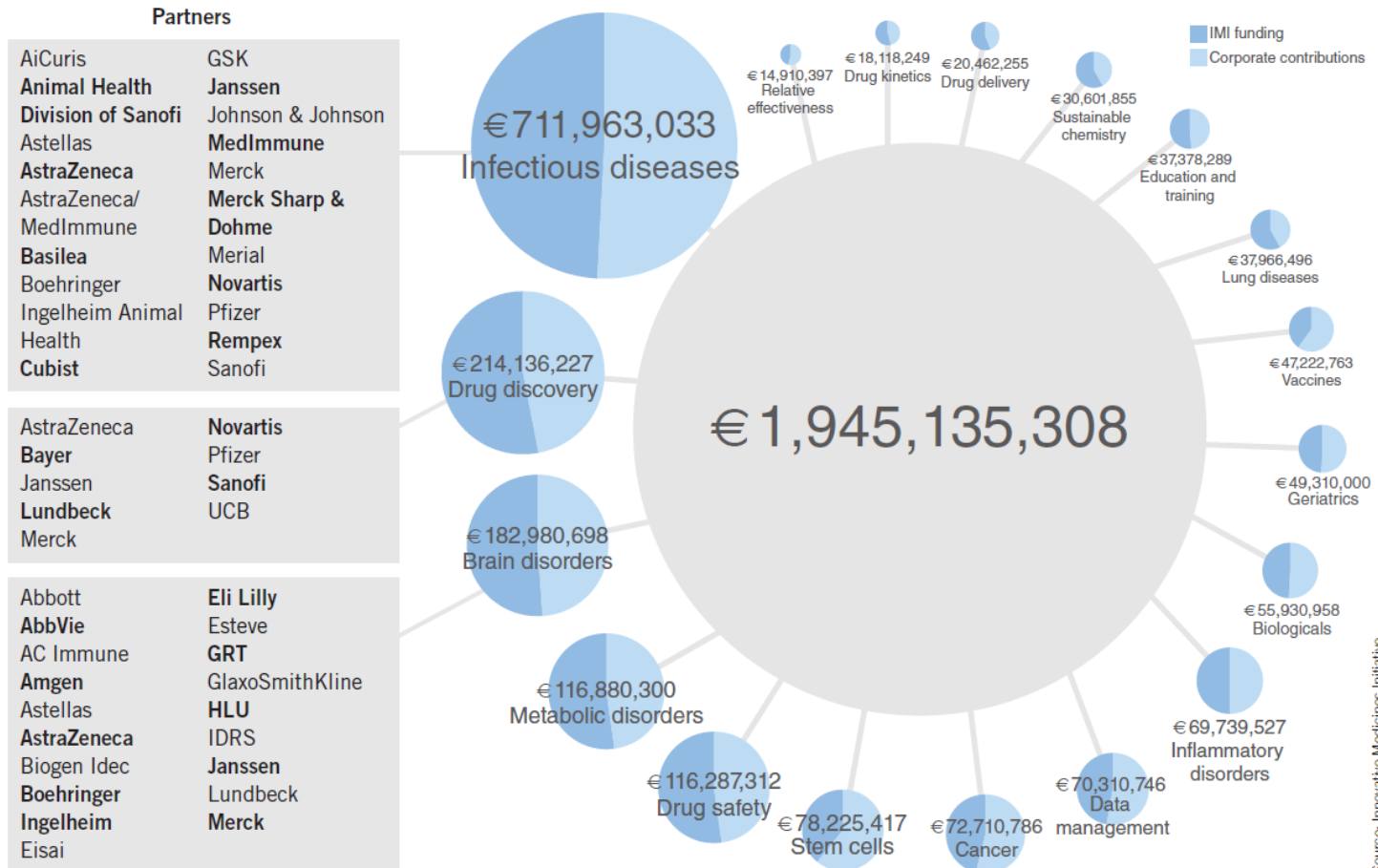
COMBACTE Online GCP In Numbers

Country	Number	%
Spain	52	39
Greece	22	16
France	9	7
Romania	8	6
Portugal	7	5
Netherlands	6	4
Albania	4	3
Hungary	4	3
Italy	4	3
Serbia	3	2
Other countries	15	11
Total	134	100

Outcome	Number	%
Passed	100	75
Failed	12	9
Not completed	22	16
Total	134	100



Infectious disease leads in first phase of Europe's IMI effort



Source: Innovative Medicines Initiative