



EU COMBACTE Consortium: Combatting bacteria multi-resistance in Europe in a public-private partnership

RON DE WINTER

19 NOVEMBER 2016

XXXVII. TÜRK MİKROBİYOLOJİ KONGRESİ



This research project receives support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115523 | 115620 | 115737 resources of which are composed of financial contribution from the European Union Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.



UMC Utrecht

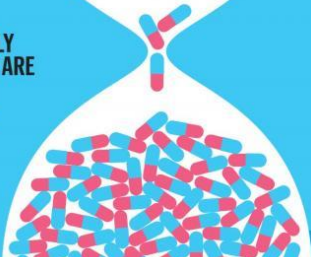
Newsweek

OCTOBER 18, 2013

THE DRUGS DON'T WORK

MORE AND MORE DEADLY PATHOGENS ARE BECOMING INCURABLE

by Kurt Eichenwald



Le Monde

La résistance des bactéries aux antibiotiques a atteint une dimension planétaire.

Antibiotic-resistant infections spread through Europe

Antibiotic resistance: we must act now, says WHO

Antibiotics resistance 'as big a risk as terrorism' – UK medical chief

The Economist

MAY 25TH - 31ST 2008

Do recoveries die, or are they killed?
Pinstriped greens take on Big Oil
Boss of the UN: worst job in the world
Win or lose, dark days for Cameron
How gangs suck El Salvador dry

When the drugs don't work
The rise of antibiotic resistance



Superbug that moves faster than science

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews



ConsumerReports

HOW TO STOP A

SUPERBUG

more and more antibiotics no longer work, and dangerous bugs are making us sicker. What can we do about it before it's too late?

HARVARD MAGAZINE

The Bacterial Menace

Antibiotic resistance spreads



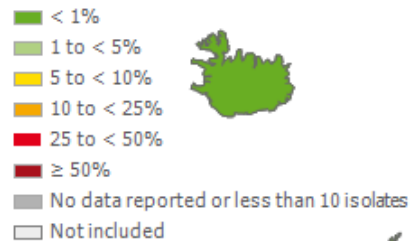
“Three million Europeans catch infections in hospital annually”

Klebsiella pneumoniae, carbapenems non-susceptible

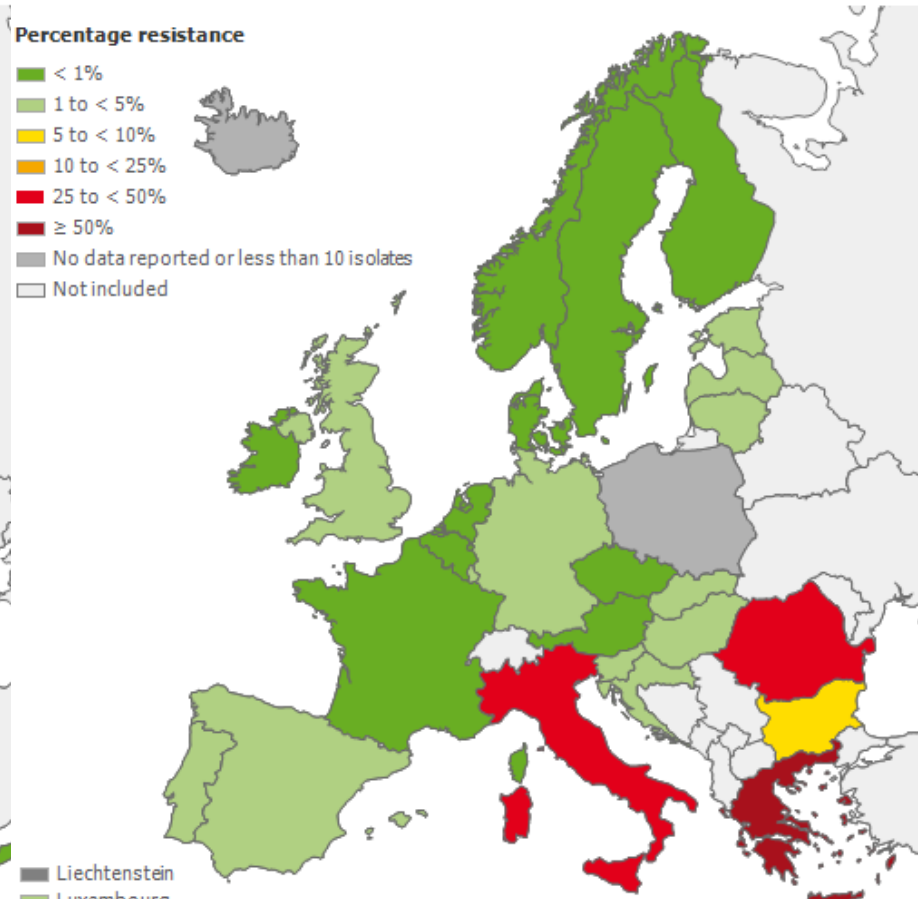
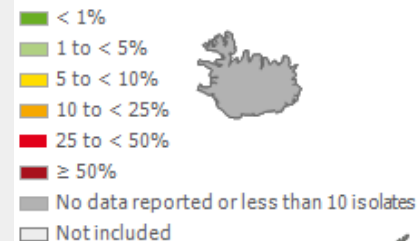
2006

2014

Percentage resistance



Percentage resistance



■ Liechtenstein
 ■ Luxembourg
 ■ Malta

■ Liechtenstein
 ■ Luxembourg
 ■ Malta

(C) ECDC/Dundas/TESSy

(C) ECDC/Dundas/TESSy



Outbreak of Colistin-Resistant, Carbapenem-Resistant *Klebsiella pneumoniae* in Metropolitan Detroit, Michigan[▽]

Dror Marchaim,^{1*} Teena Chopra,¹ Jason M. Pogue,² Federico Perez,³ Andrea M. Hujer,³
Susan Rudin,³ Andrea Endimiani,³ Shiri Navon-Venezia,⁴ Jatinder Hothi,¹ Jessica Slim,¹
Christopher Blunden,¹ Maryann Shango,¹ Paul R. Lephart,⁵ Hossein Salimnia,⁵
Deborah Reid,¹ Judy Moshos,¹ Wasif Hafeez,¹ Suchitha Bheemreddy,¹
Ting-Yi Chen,¹ Sorabh Dhar,¹ Robert A. Bonomo,^{3,6} and Keith S. Kaye¹

THE LANCET

**Emergence of plasmid-mediated colistin resistance
mechanism MCR-1 in animals and human beings in China:
a microbiological and molecular biological study**

Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang,
Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen



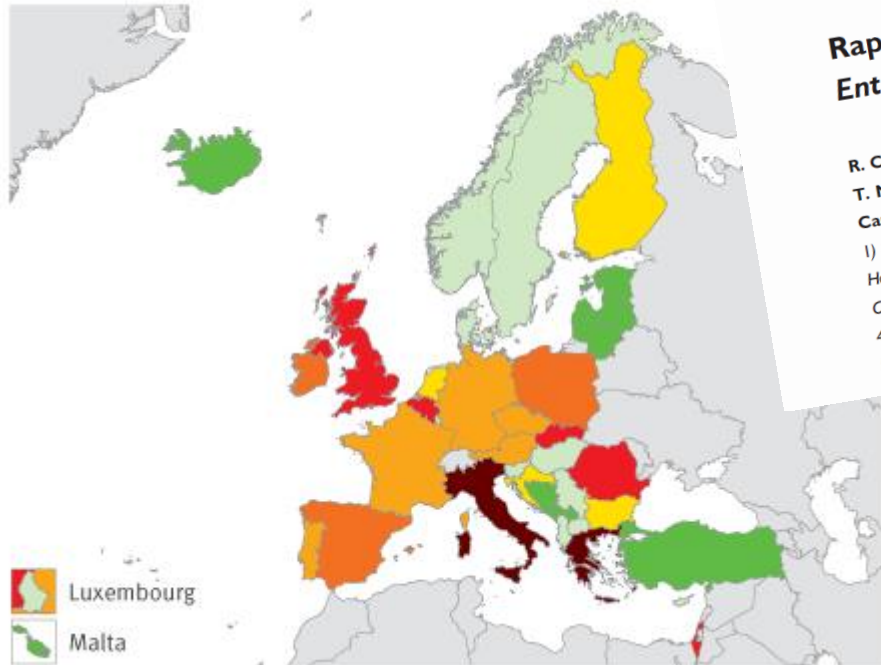
Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco^{1,2}, T. Giani^{2,3}, M. Raffone^{1,4}, F. Arena³, A. Garcia-Fernandez¹, S. Pollini³, Network EuSCAPE-Italy⁵, H. Grundmann⁶, A. Pantosti (annalisa.pantosti@iss.it)¹, G. M. Rossolini^{3,7,8}

1. Department of Infectious, Parasitic and Immune-mediated Diseases, Istituto Superiore di Sanità, Rome, Italy
2. MM and TG have equally contributed to this work
3. Department of Medical Biotechnologies, University of Siena, Siena, Italy
4. Federico II University Hospital, Naples, Italy

10.1111/j.1469-0691.2012.03821.x

A. *Klebsiella pneumoniae* carbapenemase (KPC)



REVIEW

Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe

R. Cantón^{1,2}, M. Akova³, Y. Carmeli⁴, C. G. Giske⁵, Y. Glupczynski⁶, M. Gniadkowski⁷, D. M. Livermore^{8,9}, V. Miriagou¹⁰, T. Naas¹¹, G. M. Rossolini¹², Ø. Samuelsen¹³, H. Seifert¹⁴, N. Woodford⁹ and P. Nordmann¹¹; the European Network on Carbapenemases*

1) Servicio de Microbiología and CIBER en Epidemiología y Salud Pública (CIBERESP), Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) and Hospital Universitario Ramón y Cajal, 2) Unidad de Resistencia a Antibióticos y Virulencia Bacteriana asociada al Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain, 3) Department of Medicine, Section of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey, 4) Division of Epidemiology, Tel-Aviv Sourasky Medical Centre, Tel-Aviv, Israel, 5) Clinical Microbiology MTC, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden, 6) National Reference Laboratory for Antibiotic Resistance Monitoring in Gram-negative Bacteria, CHU Mont-Godinne, Université Catholique de Louvain, Yvoir, Belgium, 7) Department of Molecular Microbiology, National Medical Institute, Warsaw, Poland, 8) National

Multi-resistant bacteria: not just a European issue

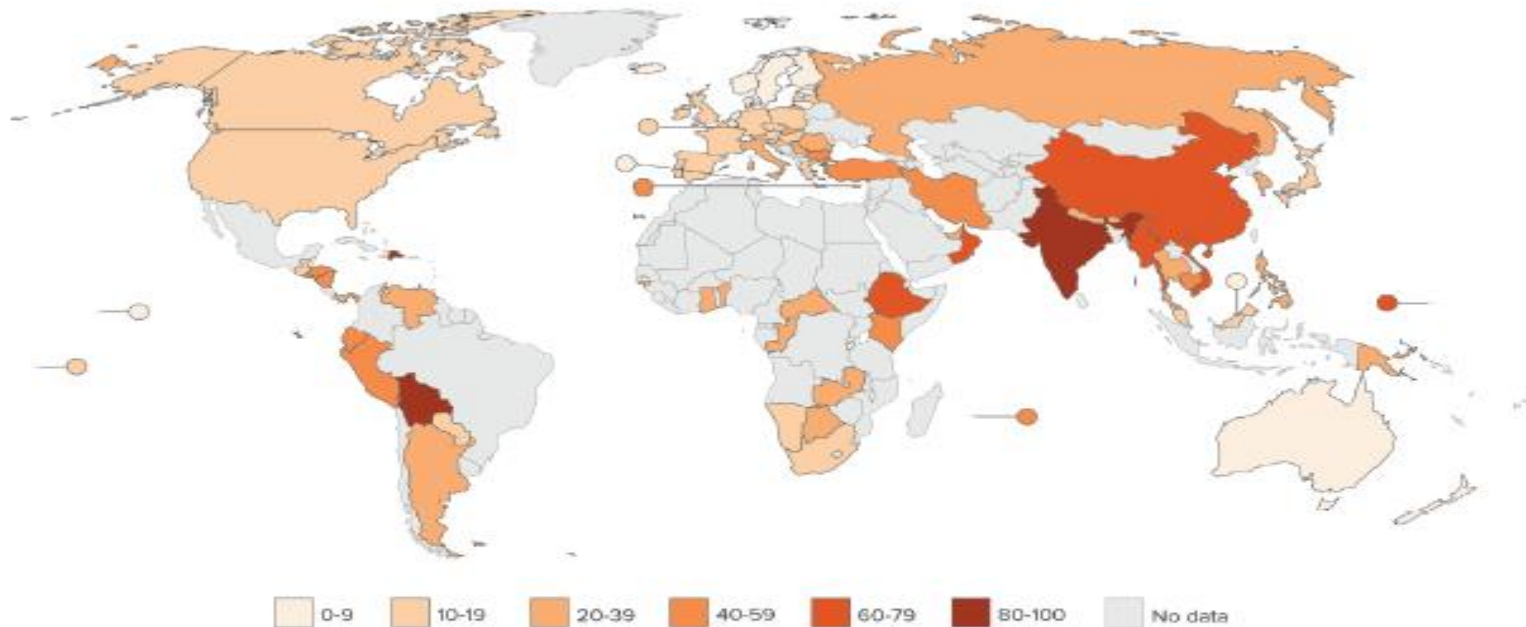


FIGURE 1-2: Percentage of extended-spectrum beta-lactamase producing *Escherichia coli, by country (most recent year, 2011–2014)**

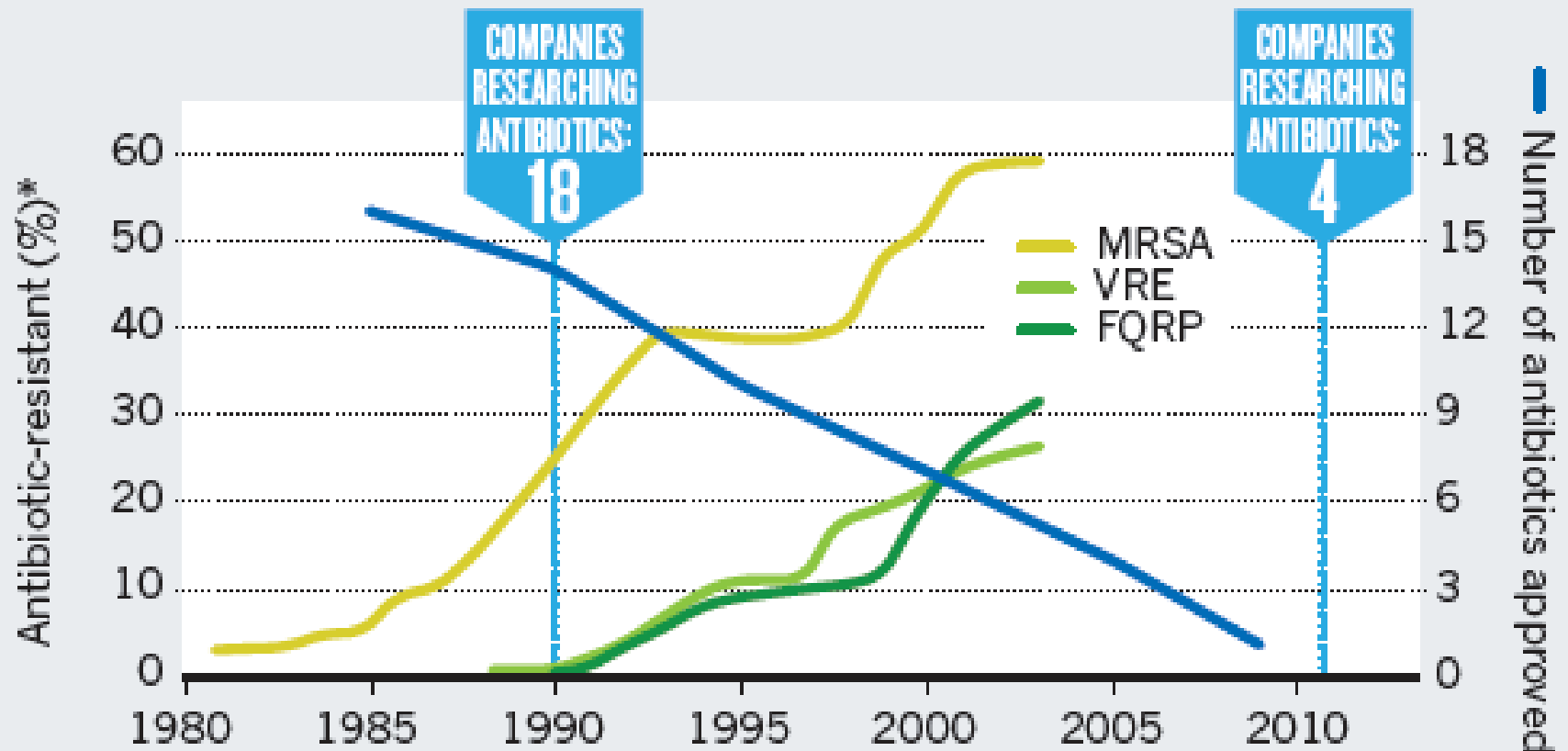
Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from invasive isolates have been used. In their absence, data from all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used: Ceftazidime, ceftriaxone and cefotaxime. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

*Indicated by third-generation cephalosporin resistance

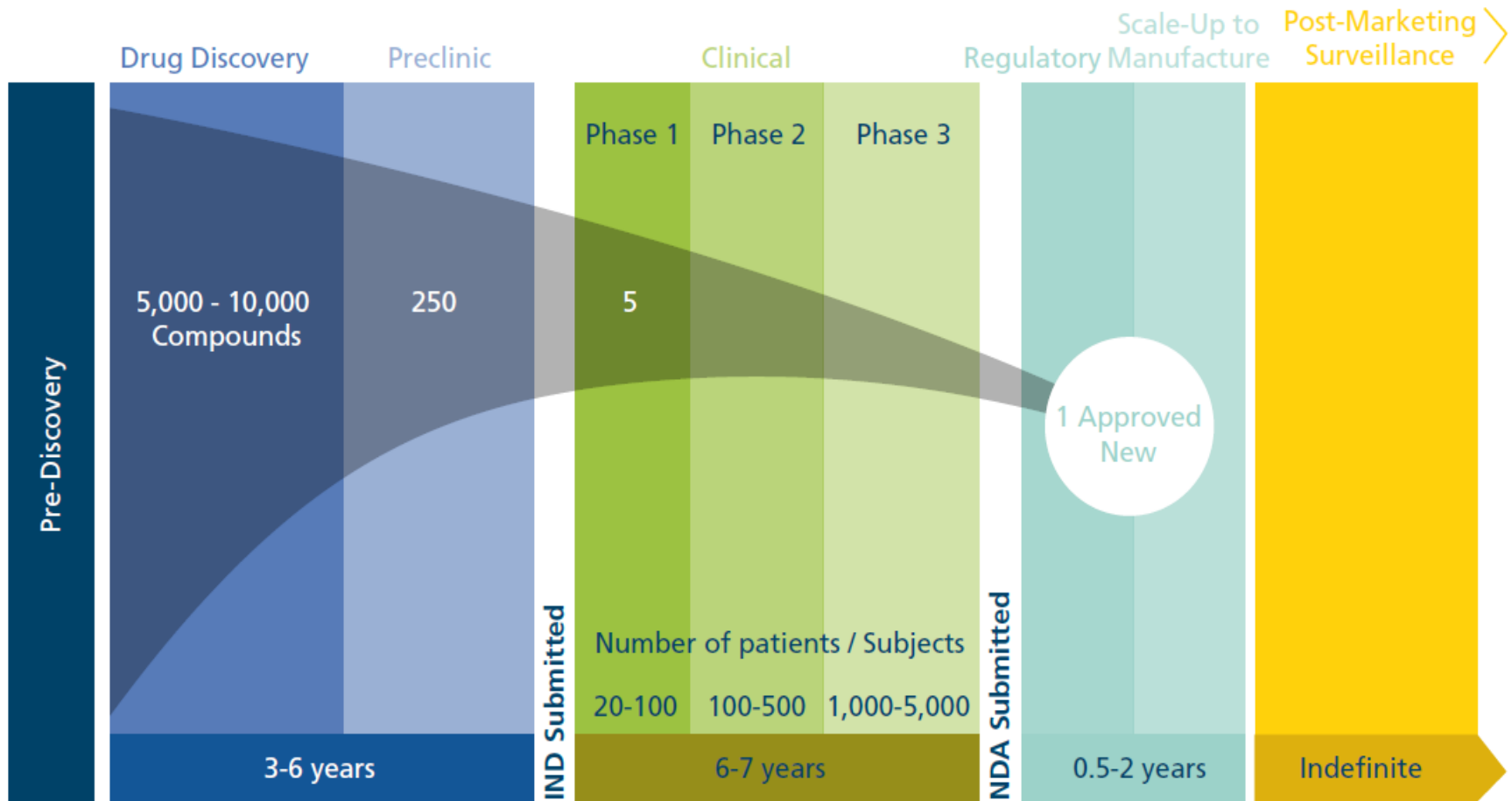
A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.



*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

Why we don't get new antibiotics



Yeni antibiyotikler ile tipik faz III alıřmaları (klinisyenin bakıř aısından)

- alıřma dizaynı her zaman memnun etmez
- Arařtırmacı ve farmasötik řirketler arası etkileřimi az
- Ana alıřmaya alt alıřmaların eklenme olasılıęı düşük
- >80% oranda tek bir hasta kaydı olmamakta
- Uzun zaman alır (en azından planlanandan daha uzun)
- Veri koleksiyonu kalitesi uygun olmayabilir



Yeni antibiyotikler ile tipik faz III alıřmaları (farmasotik řirketlerin bakıř aısından)

- Klinisyenler neden belli grnřlerin gerekli olduėunu anlamamaktadır
- Global CRO btn arařtırmacıları kiřisel olarak bildiėini belirtirler, oėu zaman doėru ıkmamaktadır
- Arařtırmacılar her zaman klinik olarak alt alıřmalarla ilgili farklı birřey istemektedir
- >80% oranda tek bir hasta kaydı olmamakta
- Uzun zaman alır (en azından planlanandan daha uzun)
- Veri koleksiyonu kalitesi uygun olmayabilir



Yeni antibiyotikler ile tipik faz III alıřmaları (klinisyen ve farmasotik řirketlerin anlařmaları)

- **>80% oranda tek bir hasta kaydı olmamakta**
- **Uzun zaman alır (en azından planlanandan daha uzun)**
- **Veri koleksiyonu kalitesi uygun olmayabilir**





Communication from the Commission to the European Parliament and the Council

Action plan against the rising threats from Antimicrobial Resistance

COM (2011) 748



ND4BB



Innovative Medicines Initiative (IMI): İş birliği için yeni bir yol

- ❖ Yaşam bilimlerinde en büyük kamu- özel ortaklığı R&D
- ❖ IMI1 başlangıcı 2008, sona erişi 2014
 - 11 Calls launched



EFPIA = European Federation of Pharmaceutical Industries and Associations

Innovative Medicines Initiative (IMI): Çalışma için yeni bir yol

❖ Ana hatlar :

- Avrupada hastalar için daha güvenli ve daha etkili ilaçların geliştirilmesini hızlandırmak
- *Avrupada biyofarmasötik sektörü geliştirmek*
- Akademi ve endüstri için iş birliği ortamı yaratır

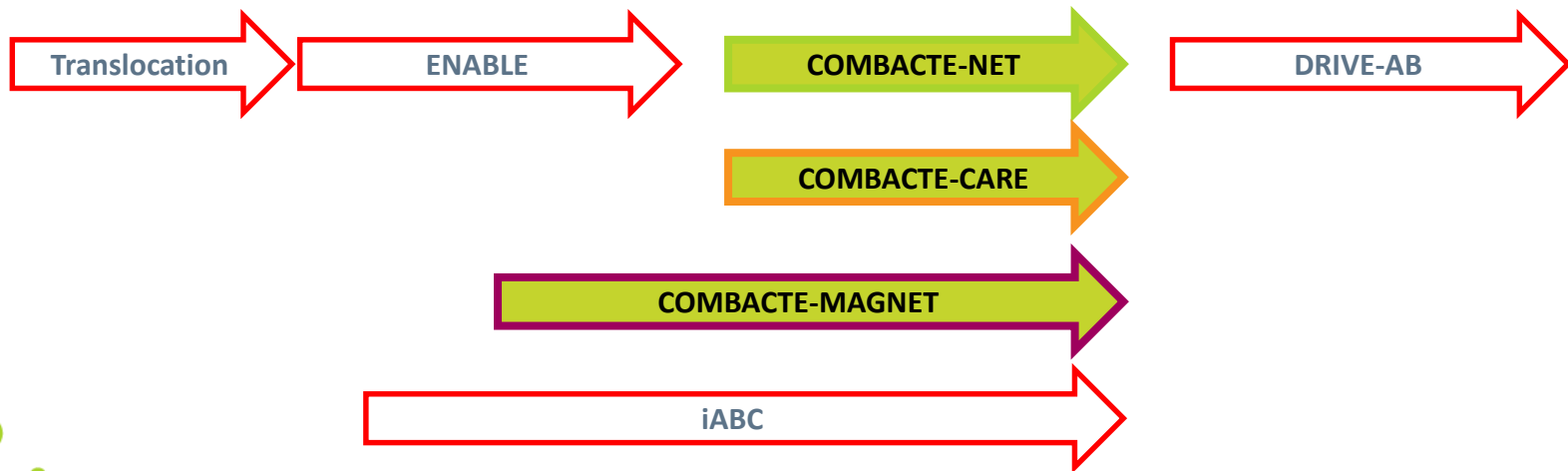
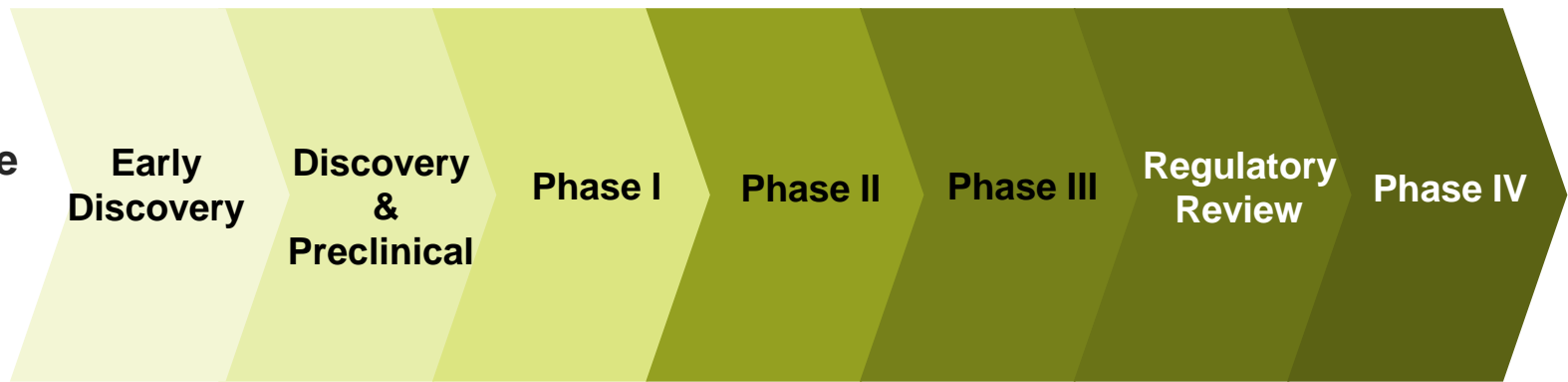
❖ **ND4BB** , Kasım 2011 de Avrupa komisyonu tarafından AMR lansmanlarının artan tehditlerine karşın eylem planının bir parçasıdır



ND4BB Vizyonu: Hastalara yeni antibakteriyal ajanları sağlama yolları

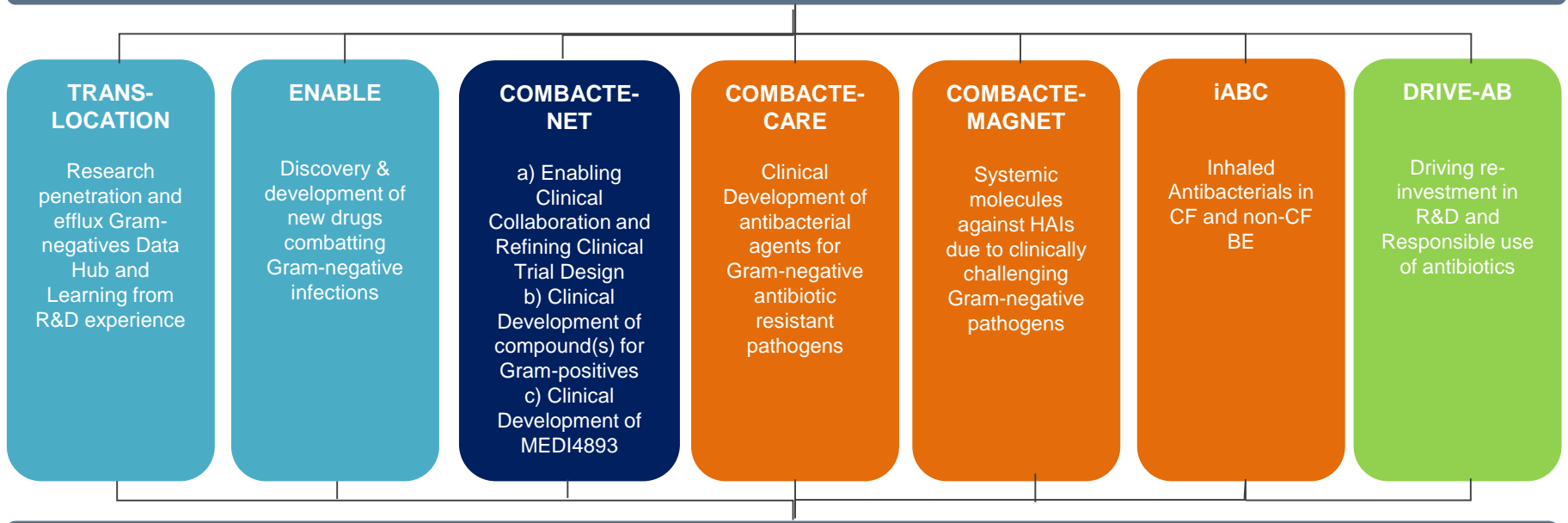
← Discovery → ← Clinical Development → ← Commercialisation →

Filling the pipeline





ND4BB Programının genel yapısı



ND4BB cross topic collaboration and dissemination



ND4BB Information Center

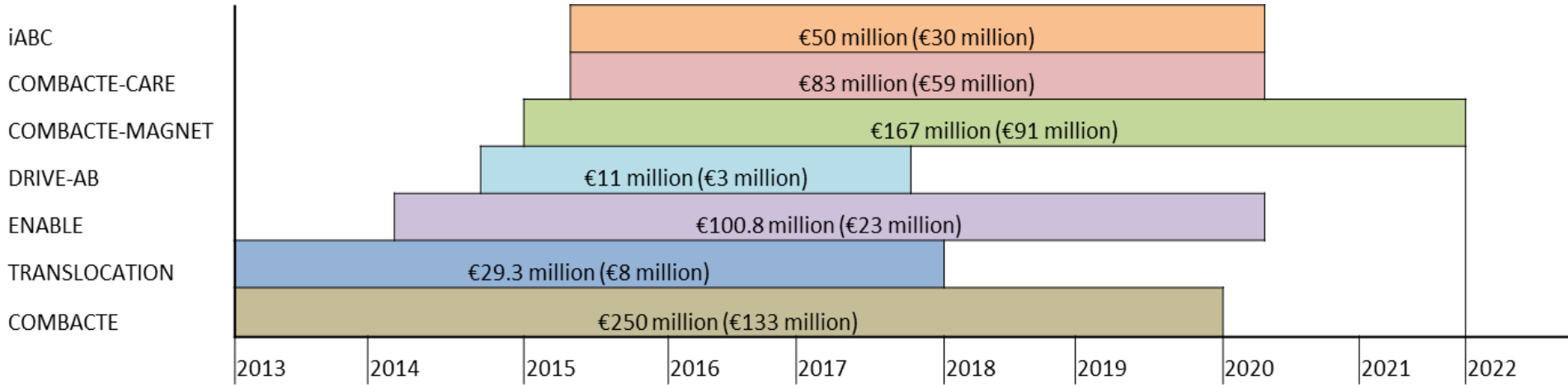
All data generated is submitted and is accessible to all consortium partners

 Drug discovery
 Drug development Gram-positives

 Drug development Gram-negatives
 Economics and stewardship



ND4BB programında 7 konunun zaman çizelgesi ve toplam bütçe tahmini (EFPIA contribution)



COMBACTE hedefleri

- ❖ **Süregelen antibakteriyal gelişim ağını yaratmak**
 - Araştırmacı merkezler ile klinik araştırmaların optimum şekilde hızlanması
 - Klinik ve epidemiyolojik veriler elde etmek
- ❖ **Antimikrobiyal ilaç geliştirme verimliliğini artırma**
 - En yeni moleküler metodolojileri ve çalışma dizaynı ile klinik araştırmaları kapsar
- ❖ **Klinik çalışmaları gerçekleştirmek**



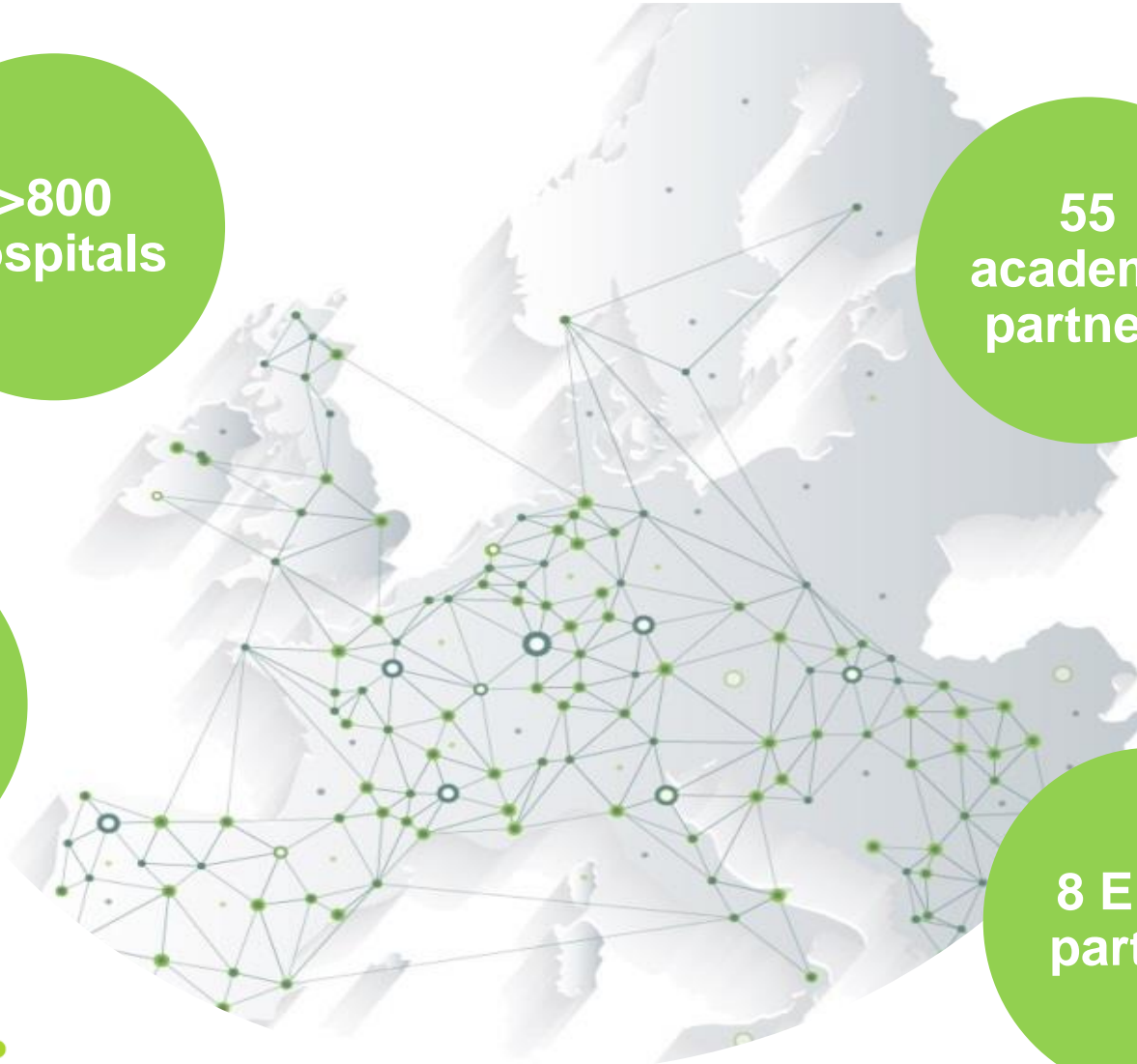
COMBACTE işbirliği

**>800
hospitals**

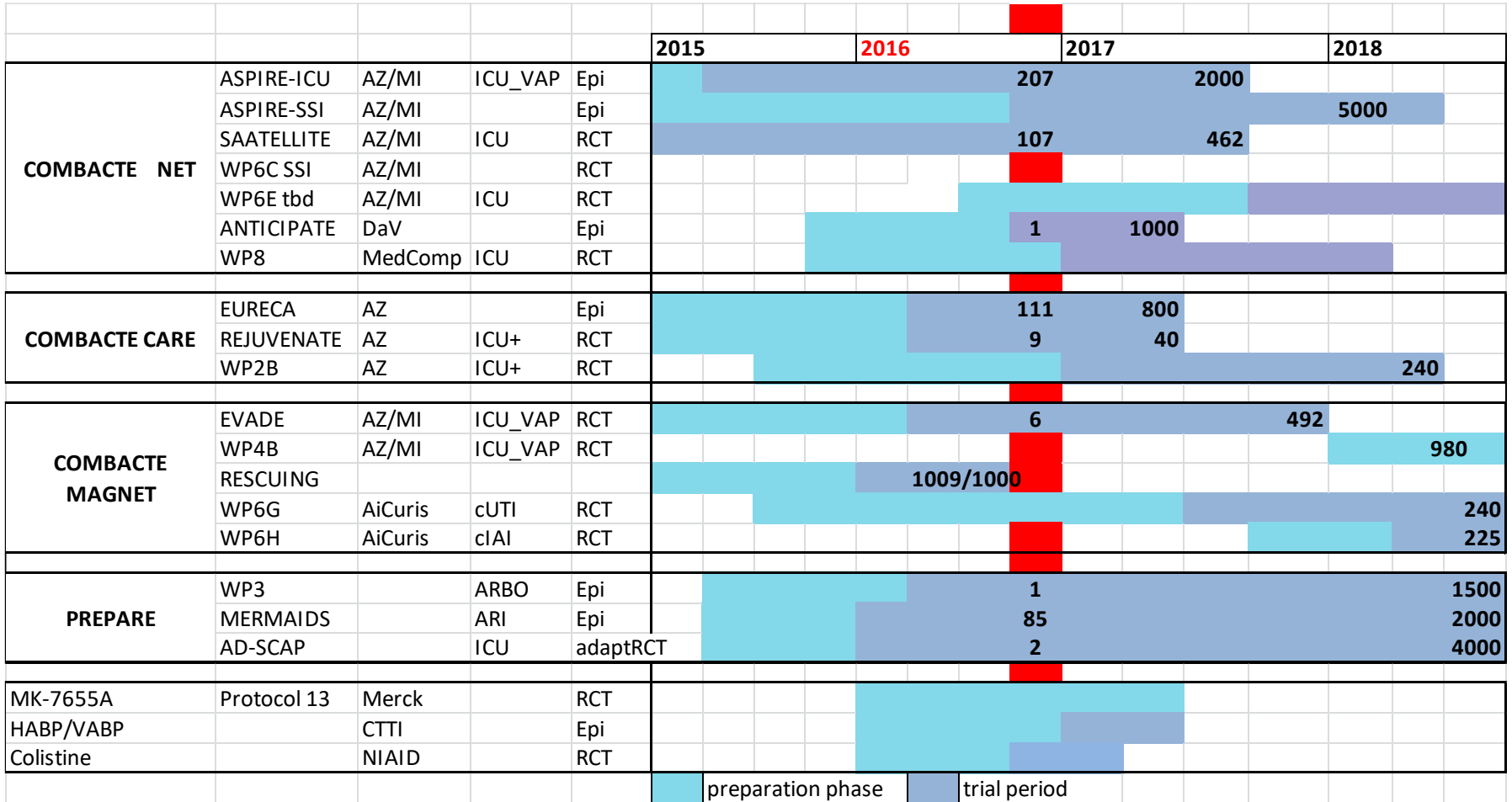
**55
academic
partners**

**42
countries**

**8 EFPIA
partners**



The COMBACTE pipeline



Total enrolled: 1,538 pts

CLINICAL TRIALS

THE 4 PILLARS OF COMBACTE



CLIN-Net

High-quality clinical research network in Europe with certification criteria and GCP Training program



LAB-Net

High-quality laboratory network in Europe with assessment of existing laboratory methods, quality assessment system, specimens and strains repository



STAT-Net

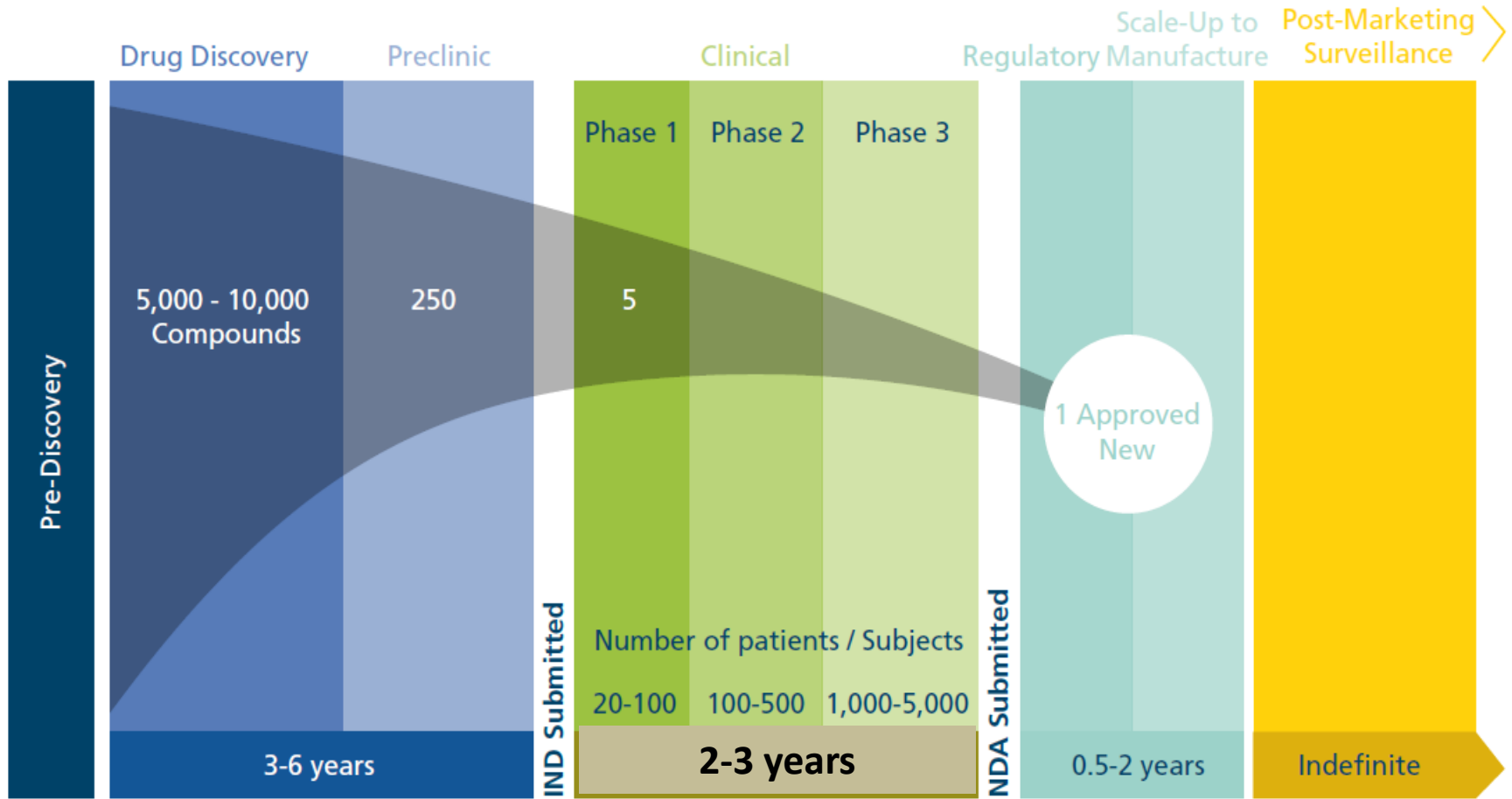
Network to improve clinical trials delivery, perform advanced biostatistical and PK/PD modelling studies, evaluate novel clinical design strategies using modern biostatistical concepts



EPI-Net

Network to identify and map existing surveillance systems, to establish frameworks for data collection to support antibacterial drug development

COMBACTE'nin hedefleri





CLIN-Net

High-quality clinical
research network in
Europe with certification
criteria and GCP
Training program

COMBACTE CLIN-Net

- ❖ The European hospital network in COMBACTE
- ❖ Complemented by the European laboratory network LAB-Net



CLIN-Net

High-quality clinical
research network in

Europe with certification
criteria and GCP
Training program

COMBACTE CLIN-Net objectives

- ❖ Develop and maintain a premier clinical research infrastructure in the field of infectious diseases
- ❖ Optimize execution of clinical studies

UMCU CLIN-Net üyeleri



CLIN-Net

Academic lead



Marc Bonten

Head of PMO



Ron de Winter

Medical coordinator



**Miquel
Ekkelenkamp**

**Organisation
coordinator**



Miranda Hopman

CLIN-Net team



**Nienke
Cuperus**



**Katina
Kardamanidis**



**Sophie
Corthals**



Belmira Behlić



**Claire-Marie
Martis**

CLIN-Net alıřmaları

- Merkez deęerlendirme ve seimi
- alıřma desteęi
- Eęitim
 - Good Clinical Practice (GCP)
 - Site-trainings
- Gvenilir uluslararası iřbirlięinin kurulması ve devamlı bir hale getirilmesi



CLIN-Net

CLIN-Net infrastructure

CLIN-Net PMO





CLIN-Net

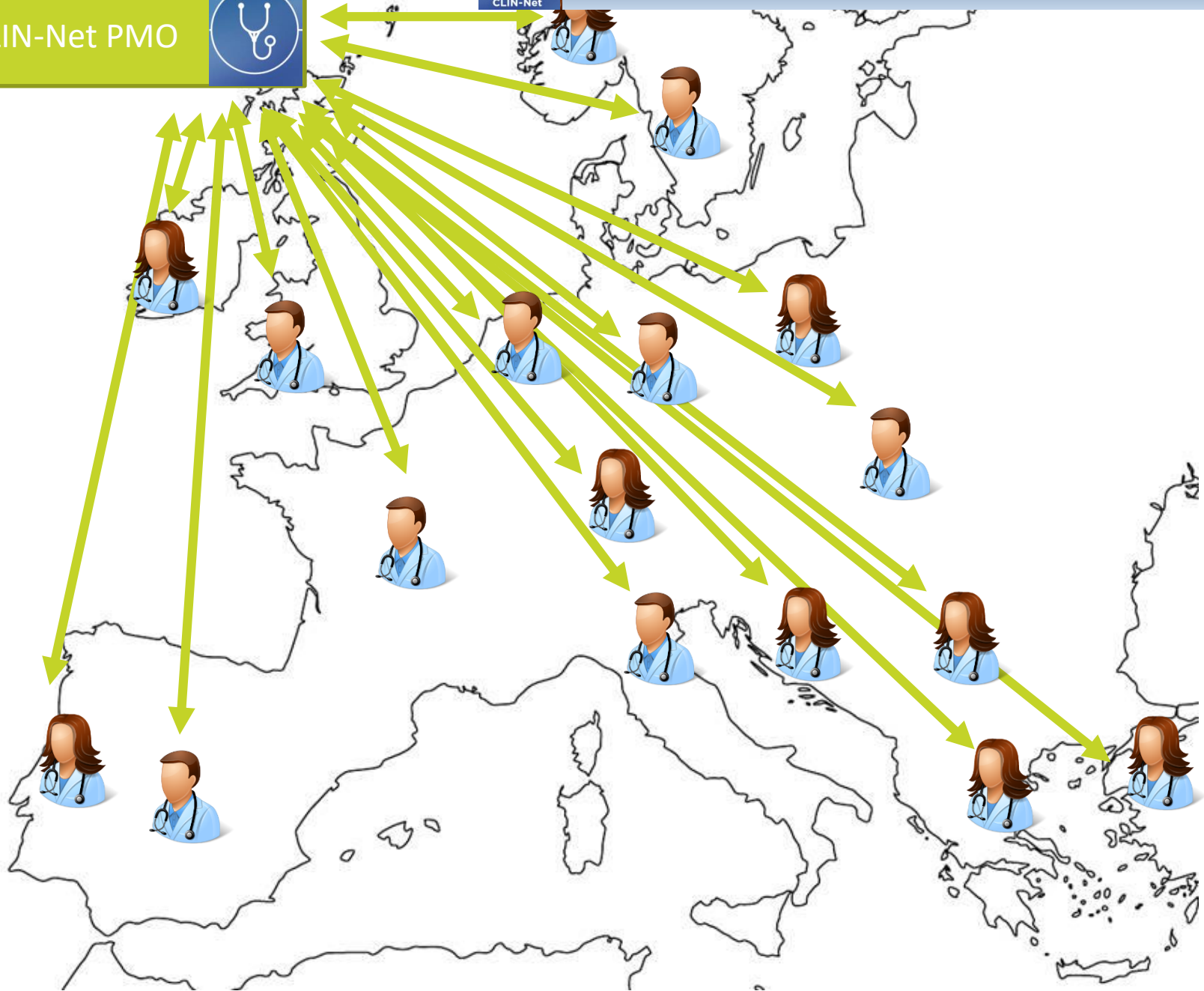
CLIN-Net infrastructure

CLIN-Net PMO 



CLIN-Net infrastructure

CLIN-Net PMO



CLIN-Net PMO



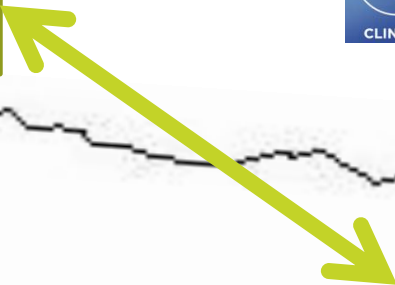
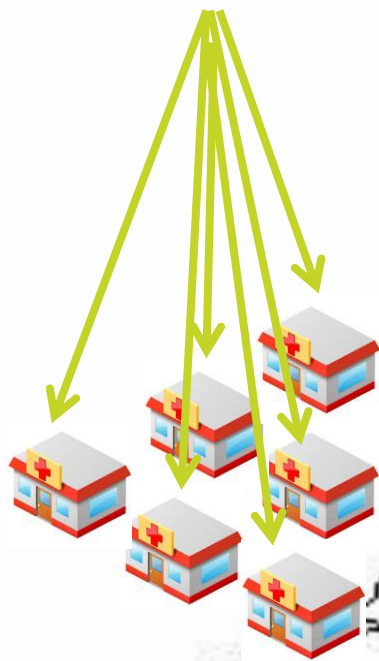
CLIN-Net infrastructure



CLIN-Net PMO



CLIN-Net infrastructure



CLIN-Net PMO



LAB-Net PMO

Regional team

Main contact person

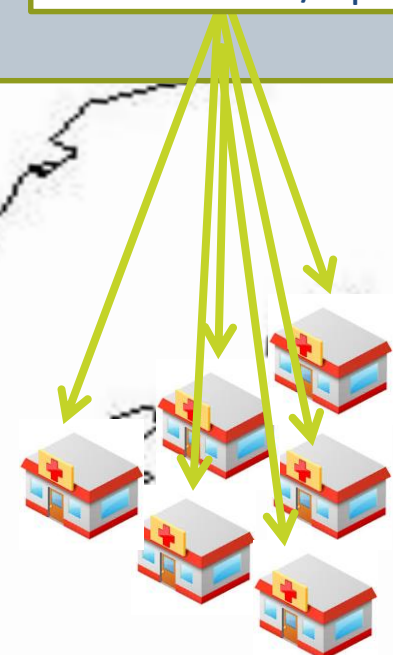
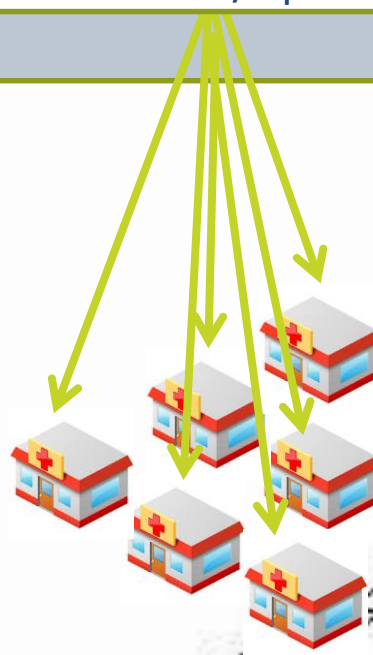
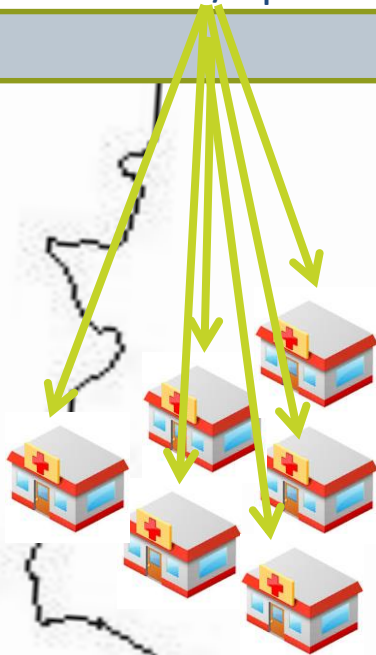


LAB-Net coordinator

Coordinator 1
subnetwork / specialty

Coordinator 2
subnetwork / specialty

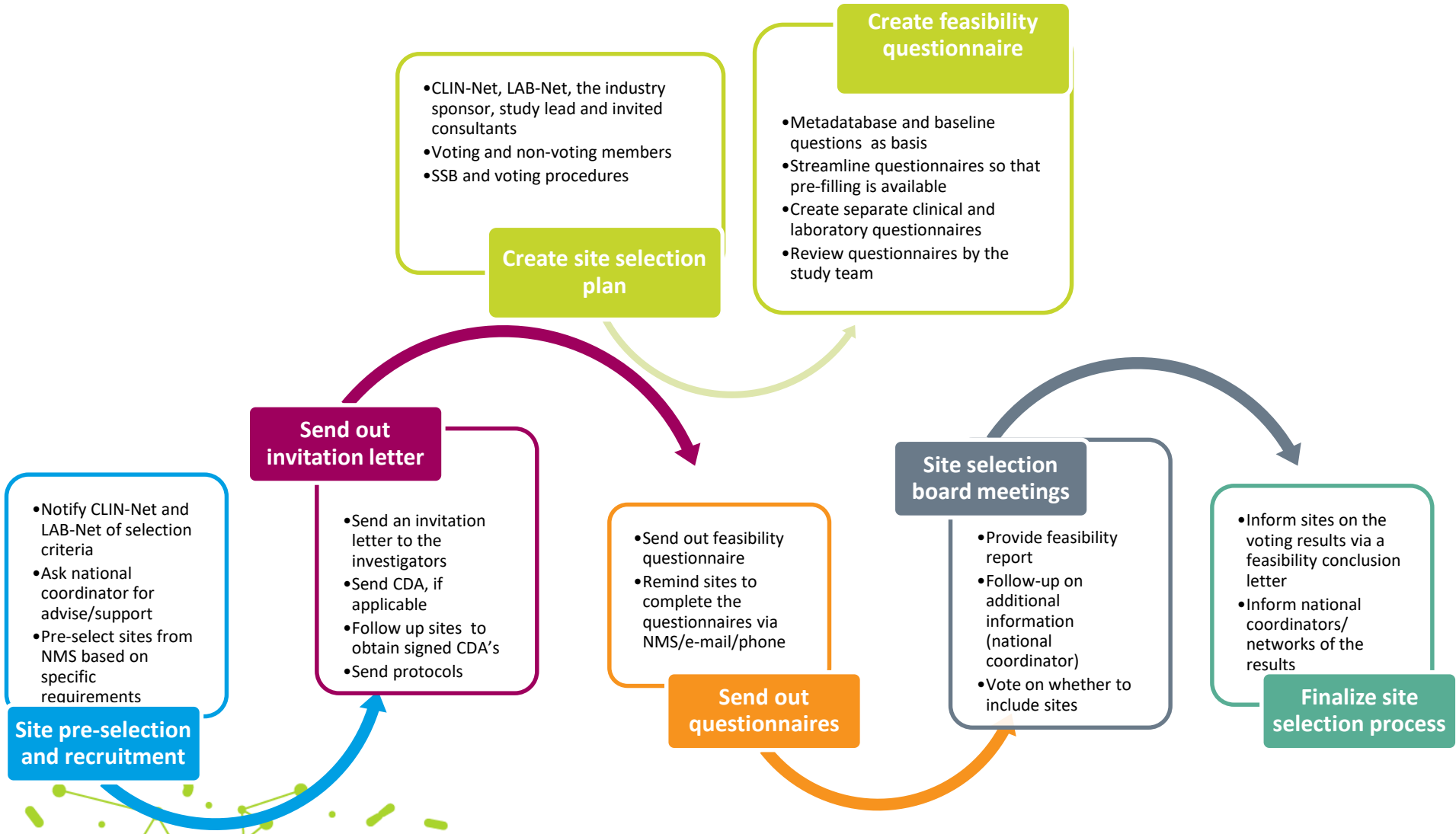
Coordinator 3
subnetwork / specialty



CLIN-Net

CLIN-Net infrastructure

CLIN-Net merkez seçim işlemleri



Fizibilite anketleri

- Clinical and laboratory feasibility questionnaires are created based on a list of requirements for clinical sites and local laboratories

NIH Colistin Trial

<i>Study</i>	<u>Combacte</u>	<i>Subject</i>	_____
<i>Form version</i>	<u>7</u>	<i>Inclusion date</i>	_____
<i>Form status</i>	_____	<i>Site</i>	_____
<i>Last saved date</i>	_____		
<i>Last saved by</i>	_____		

This questionnaire will take approximately 25 minutes to complete. Please note: for some questions, information needs to be retrieved from your medical records, laboratory database or pharmacy. Therefore, the questionnaire allows you to save the information already entered and to continue later. By using the same URL/web address, you will be able to continue where you left off. Consent The responses to the questionnaires, which include your personal data and data relating to the institution of which you are an employee, will be stored in a database. By submitting this questionnaire, you: a) Consent to the storage and processing of your responses; b) Warrant that this (personal) data is correct; c) Warrant that the institution consents to submitting the data in the questionnaires; d) Consent to the possibility CLIN-Net might contact you in the future regarding projects CLIN-Net might be involved in. You will at all times retain the right to withdraw your consent.

Access The database is only accessible to COMBACTE CLIN-Net. However, you will have access to your own personal data and data that relates to the hospital / institution of which you are an employee. You have the right to correct the information stored in the database.

Protection of (personal) data COMBACTE CLIN-Net has implemented appropriate technical and organizational measures to protect (personal) data against loss or any form of unlawful processing.

Privacy The processing of (personal) data by CLIN-Net will be in accordance with applicable laws and regulations regarding privacy, such as the Dutch Personal Data Protection Act and the European Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

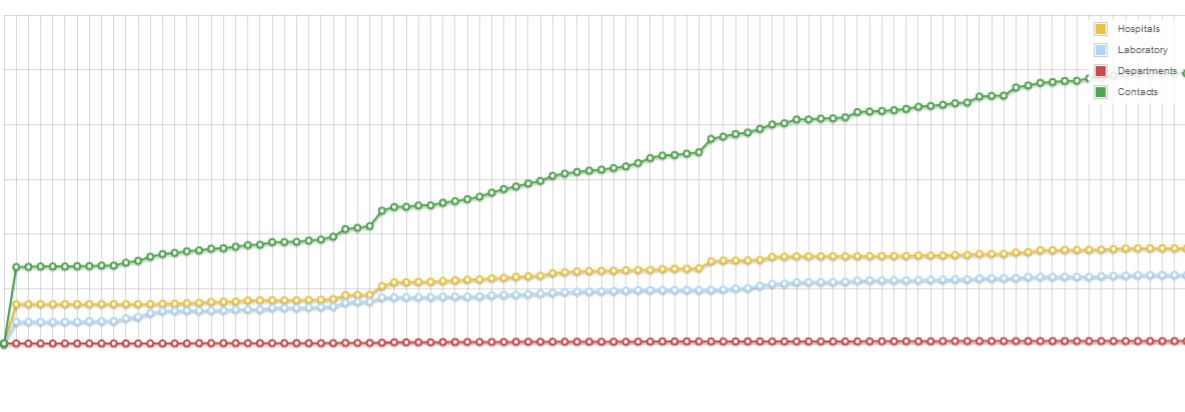
I understand and want to continue the questionnaire

Yes

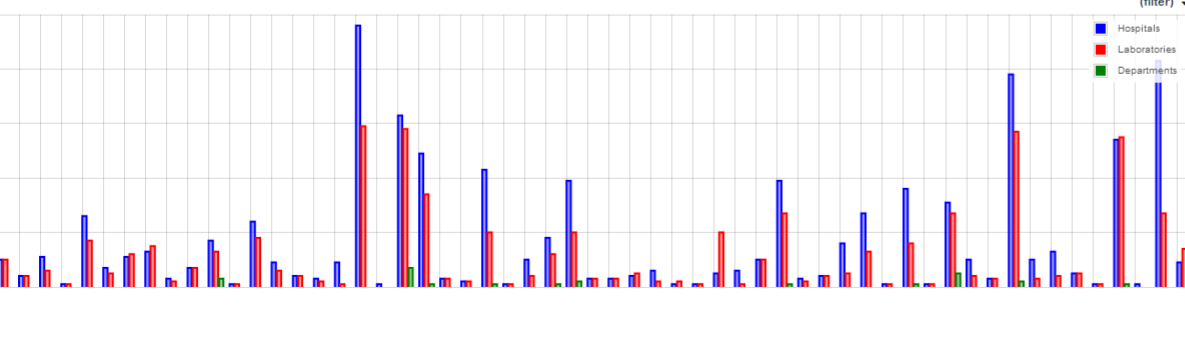
No

Bazi raporlar:

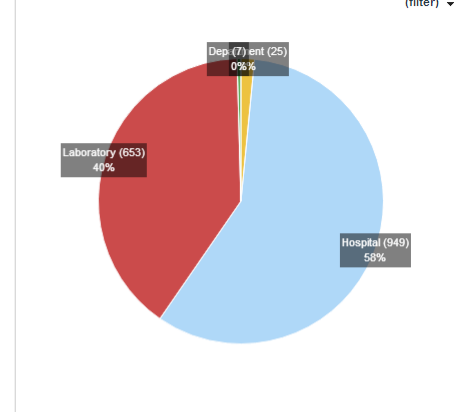
Organizations Historical Growth



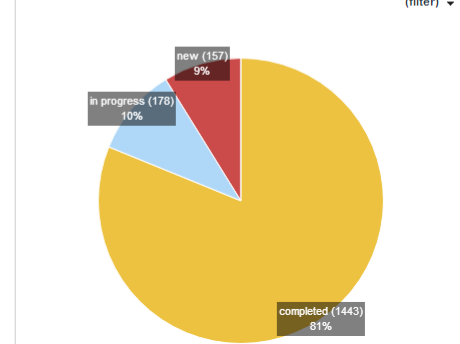
Organizations by Type / Country



Organizations by Type



Questionnaires by Status



Önceden doldurulmuş anketler



[Home](#)

[Switch active study](#)

[My Account](#)

[Administration](#)

[Study configuration](#)

[Research](#)

[Reporting](#)

Institution Name

University medical center Utrecht

Department

Julius Center

Address

Heidelberglaan 100

City

Utrecht

Postal code

3454 RD

Country

The Netherlands



Merkezlerin önseçimi ve denemeleri

CLIN-Net ve LAB-Net, devam eden çalışmanın özel gereksinimlerine dayanarak seçilmiş merkezlerin bir başlangıç listesini oluşturur.

1. Based on information COMBACTE has on a large and growing number of hospitals aligned with laboratories in the COMBACTE Network Management System (NMS).
2. Ask national network coordinator(s) to pre-select sites within their network based on their experiences with the sites.



School of Medicine

Dear Dr. Emanuele Durante Mangoni,

We would like to formally invite you to participate with University of Naples S.U.N./Monaldi Hospital in a "Randomized Controlled Trial for the Treatment of Extensively Drug-Resistant Gram-negative Bacilli". This trial is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) in the United States of America, and funded by the National Institutes of Health.

Invitation letter with link



Fizibilite anketleri

Organization Name	Organization Type	Questionnaire Status	Country	Study Group	Report	Organization	Type	ASPIRE SSI CLIN	ASPIRE SSI Lab	Bas elime clin	Bas elime lab	CREDIBLE clin	CREDIBLE lab	CTTI	EURECA clin	EURECA lab	EVADE	Historical Bas elime clin	NIH Colistime Trial clin	NIH Colistime Trial lab	PREPARE WP2	PREPARE-WP5 AD SCAP	PREPARE_WP7 lab
			Italy		Export to Excel	Azienda Ospedaliera Universitaria Integrata	Hospital																
						Azienda Ospedaliera Universitaria Senese	Hospital																
						Azienda Ospedaliera – University of Padova	Hospital																
						Azienda Ospedaliero- Universitaria di Udine	Hospital																
						Azienda Ospedaliero-Universitaria Ospedali Riuniti Ancona	Hospital																
						Azienda Ospedaliero-Universitaria Pisana	Hospital																
						Azienda Sanitaria Locale Ospedale Di Venere Bari	Hospital																
						BRESCIA Hospital	Hospital																
						Clinica di Malattie dell'Apparato Respiratorio, Arcispedale S. Anna	Hospital																
						FIRENZE Careggi Hospital	Hospital																
						Florence University Hospital	Hospital																
						Hospital Luigi Sacco	Hospital																
						IRCCS Fondazione Ca Granda Ospedale Maggiore Policlinico	Hospital																
						Molinette Teaching Hospital	Hospital																

Çalışma grupları

Per Organization **Per Country**

Organization Name

Study Name

Country

Export to CSV

Organization	Type	Country	ANTICIPATE	ASPIRE-ICU	ASPIRE-SSI	CREDIBLE	CTTI	EURECA	EVADE (MAGNET WP-4A)	NIH Collis tin
AAA_ALBANIE TEST SITE!!!	Hospital	Albania								
APHP Beaujon	Hospital	France	✓							
APHP Bichat	Hospital	France	✓							
APHP St Louis	Hospital	France	📁							
Attikon University General Hospital	Hospital	Greece	–							📁

Members



1 to 20 of 91

Name	Organization	Type	Role	Email	Phone	Country
Muriel Fartoukh	APHP Tenon	Hospital	Principal Investigator	muriel.fartoukh@aphj		France
Guillaume Arlet	APHP Tenon	Laboratory	Laboratory lead	guillaume.arlet@aphj		France
Guillaume Voiriot	APHP Tenon	Hospital	Sub-investigator	guillaume.voiriot@tnr		France
Amel Touati	APHP Tenon	Hospital	Research nurse	amel.touati@aphp.fr		France
F.J. Schuitemaker	Amphia Hospital	Hospital	Sub-investigator	FSchuitemaker@amj		Netherlands
Debbie Arens	Amphia Hospital	Hospital	Research nurse	DArens@amphia.nl		Netherlands
Willeke Bieze	Amphia Hospital	Hospital	Research nurse	WBieze@amphia.nl		Netherlands
Jannie Romme	Amphia Hospital	Hospital	Research nurse	JRomme@amphia.nl		Netherlands
Wendy Herijgers	Amphia Hospital	Hospital	Research nurse	WHerijgers@amphia		Netherlands
Peter van Keulen	Amphia Hospital	Laboratory	Principal Investigator	pvkeulen@amphia.nl		Netherlands

The COMBACTE Merkez seçim masası

- **Fizibilite anketlerinde verilen bilgiler temelinde SSB merkezleri değerlendirir :**
 - Seçilen merkez
 - Yedek merkez
 - Seçilmeyen merkez
- **Her merkez bir “karar mektubu” gönderilerek bilgilendirilir**
- **Ulusal koordinatörlere ülkelerindeki seçim bölgesi ve seçim sürecinin sonuçları hakkında bilgi verilir**



Çalışma bilgisi ve süreci

Selected Study: ASPIRE-ICU

Selected Organization: UMC Utrecht

General **Site Milestones** Actual

Site status: active recruiting

Name monitor: tbd

Email monitor: tbd

Phone monitor:

Date clinical FQ sent: 16/04/2015 The send date, reminders and completed date are automatically filled based on the associated Questionnaire

Nr reminders clinical FQ: 0

Date FQ completed: 16/04/2015

Date site selected: 01/09/2015 Selection Status: Selected

Selection Status Comment:

CDA sent date: 01/10/2015 CDA signed date: 07/10/2015 Nr days btwn CDA sent date and CDA signed date: 6

contract sent: 07/10/2015 date contract signed: 30/10/2015 days between contract sent and contract: 23

General **Site Milestones** Actual

	Expected number	Actual number
no of subjects planned	100	72
no of subjects screened	1000	699
no of subjects screen failure	900	627
no of subjects enrolled	100	72
no of subjects randomized	0	0
no of subjects drop out	0	0
no of subjects completed	100	0

GCP in COMBACTE

- Adequate training in GCP essential for reliable execution of trials
- **COMBACTE will (in the near future) require all personnel actively involved in studies to be GCP compliant**
 - Basically: all people obtaining informed consent and completing research files (CRFs)
- **CLIN-Net GCP-training complies with TransCelerate requirements**
 - Also with PharmaTrain requirements (EU accreditation) and EU directives and regulations
- **Where feasible and necessary, obtaining national or EU accreditation (CME) is sought for its courses**
 - If solicited by participants / national coordinator



Online GCP Kursu

Partnership with Elevate Health, a company specialized in online education, to develop an interesting, online GCP Course

- Interactive, e-moderator
- Takes 6 to 8 hours to complete, must finish within one calendar month
- Compliant with TransCelerate and PharmaTrain requirements



Hello, I am dr. Whitmore. I am the investigator during the clinical trial you will be reading about in the following Learning Units. According to ICH-GCP, an investigator is:
'A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.'

As a principal investigator I can supervise so-called subinvestigators. According to ICH-GCP, a subinvestigator is 'any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows)'.

F2F eğitimi: EF-GCP ile işbirliği

- 1 or 2-day training
- Since our last meeting:
 - Belgrade
 - Budapest
 - Madrid
 - Athens
- In planning: Sofia
- Others: when requested by investigators / NC



Investigators GCP trained by CLIN-Net

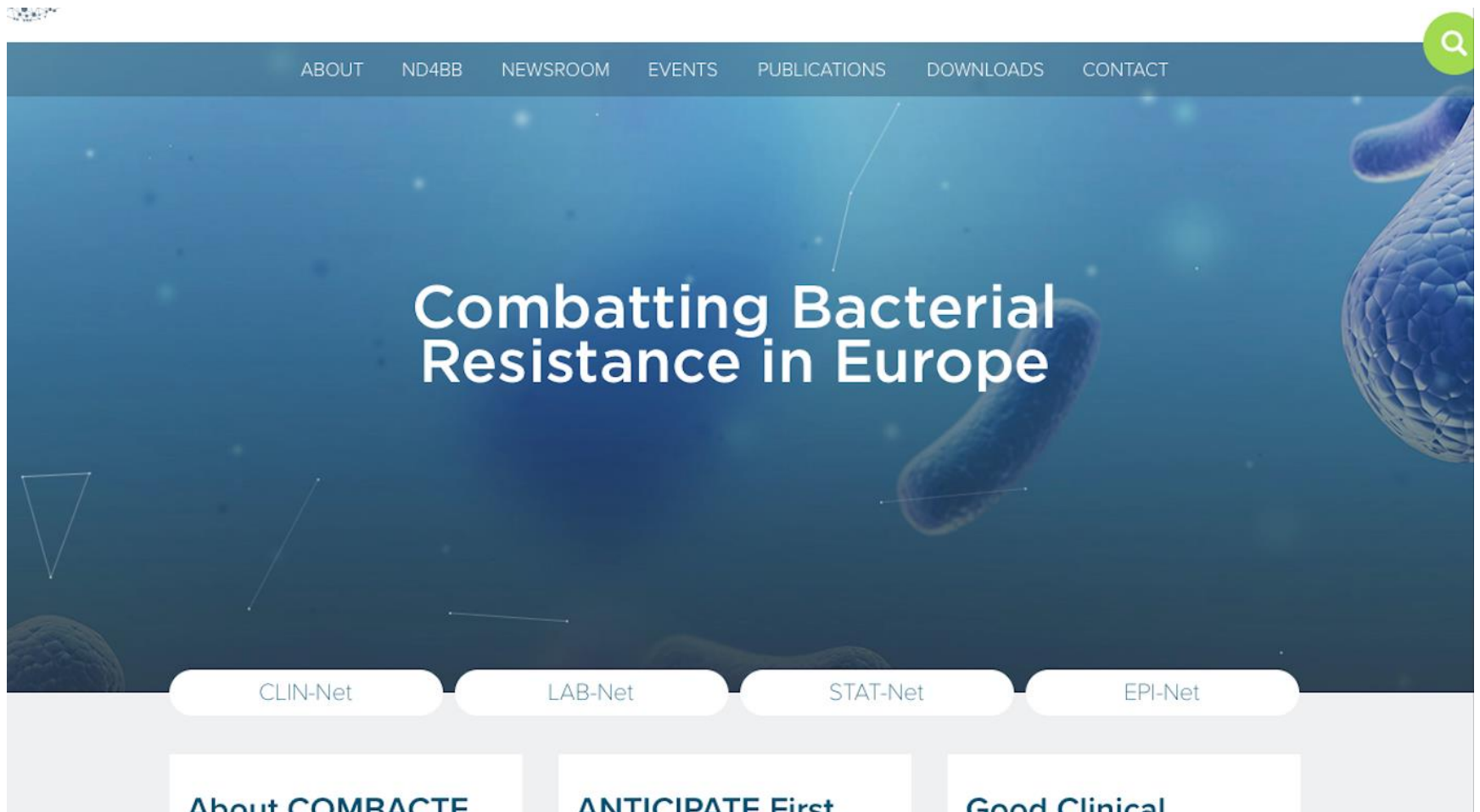
Year	Online GCP course	Face to face GCP courses
2016	108	102
2015	96	55
2014	38	22
Total	242	179

Diğer iletişim kanalları

- Ulusal koordinatörler ile
 - Country visits
 - Quarterly updates to NC
- Diğer katılımcılar ile
 - Yearly ECCMID-meeting
- Kamu ile
 - Website and newsletter
 - New: Dashboard on website
 - Magazine
 - Presence at meetings



Website: www.combacte.com



Çalışma gösterge tablosu



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About this study

Study information

Study No:	NA
Study Name:	ASPIRE-ICU
Test Article:	NA
Study Type:	Observational
Study Status:	Active
Enrollment Period:	Jun2015 - Sep2017

Subject screening and enrollment

Total Subjects Planned:	2000
Total Subjects Screened:	1604
Total Subjects Enrolled:	241
Enrollment Completed:	12,05%

Site selection

Nr countries planned:	11	Nr sites planned:	30	Nr sites initiated per country:	19
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Sorular ?

