Building a European clinical research alliance to respond to emerging infectious diseases

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PREPARE, COMBACTE LAB-Net and VALUE-Dx Coordinator, University of Antwerp

ECRAID-Plan Coordinator, University Medical Center Utrecht
Hope you will see the light in the tunnel at the end of my talk!
“There are only two infectious disease situations that can be considered inevitable, serious pandemic threats: influenza and antimicrobial resistance”

Osterholm and Olshaker,
Diedliest enemy: our war against killer germs, March 2017.
1. PREPARE:
Preparation Europe for Infectious Diseases outbreaks and pandemics
PREPARE: Platform for European Preparedness Against (Re-)emerging Epidemics

2014-2021
Partners:
Academia, clinical trial networks, industry societies

Coordinator:
Herman Goossens
(University of Antwerp)

Deputy Coordinator:
Menno de Jong
(Academic Medical Center Amsterdam)

Our mission
To establish PREPARE as the European clinical research framework
• for harmonised large-scale clinical research studies on infectious diseases
• prepared to rapidly respond to any severe infectious disease outbreak
• providing real-time evidence for clinical management of patients and for informing public health responses
Overall architecture

PATHOS: European platform for patient-oriented PATHOgenesis Studies

PRACTICE: Platform for Harmonised and Rapid response Clinical Trials in Infectious diseases in Children and adults in Europe

PREDICT: European Platform for REsearch and support on Diagnostics for Infectious disease Clinical Trials

CRISP: Clinical Research Information Sharing Platform

CREATE: Clinical Research Education And Training in Europe

Funded by the European Union
Clinical studies in PREPARE

Three observational studies: Multi-centre EuRopean study of MAjor Infectious Disease Syndromes (MERMAIDS) in primary care and hospitalized adult and pediatric patients, comprising:
- Sepsis-like syndrome (SLS) in infants and Acute respiratory infection (ARI) in children (PED-MERMAIDS)
- Acute Respiratory Infections in Adults (ARI)
- Arboviral compatible febrile illness

Two Adaptive platform design studies:
- European multi-centre double-blinded randomised placebo-controlled Interventional Trial on Influenza-Like-Illness (ILI) in Primary Care (ALIC4E)

- Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP)

Funded by the European Union
Adaptive Platform Trials

Many advantages:
- Focus on disease, not a particular Rx
- Multiple interventions (arms)
- ‘Perpetual’ enrollment
- Often based on Bayes’ theorem
- Tailor choices over time
- Add and substitute arms in the event of a pandemic Respiratory Tract Infection
- Emphasis on efficiency with (very) small sample sizes
- Different therapies “graduate” to next phase while trial continues

Berry et al JAMA 2015
Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial

Christopher C Butler, Alike W van der Velden, Emily Bongard, Benjamin R Saville, Jane Holmes, Samuel Coenen, Johanna Cook, Nick A Francis, Roger J Lewis, Maciek Godycki-Cwirko, Carl Llor, Sławomir Chlabicz, Christos Lionis, Bohumil Seifert, Pär-Daniel Sundvall, Annelies Colliers, Rune Aabenhus, Lars Bjerrum, Nicolay Jonassen Harbin, Morten Lindbæk, Dominik Glinz, Heiner C Bucher, Bernadett Kovács, Ruta Radzевичiene Jurgute, Pia Touboul Lundgren, Paul Little, Andrew W Murphy, An De Sutter, Peter Openshaw, Menno D de Jong, Jason T Connor, Veerle Matheeussen, Margareta Ieven, Herman Goossens, Theo J Verheij

The Lancet, in press
Funded by the European Union

REMAP-CAP

• **Funding:**
  – EU FP7 PREPARE WP 5 program
  – Australian NHMRC ‘OPTIMISE’ program ($6M)
  – New Zealand NRC ($2M)
  – Applications submitted elsewhere

• **Simultaneously test:**
  – Different anti-microbial strategies
  – Different host immunomodulation strategies
  – Different ventilation strategies

• **Separate RAR and stopping rules for multiple subgroups**

• **Patients are preferentially assigned to the best performing arm**
  – Allocation is random, bit not 50:50
  – Odds of assignment proportional to odds of success
The outbreak research modes of PREPARE

0. Default Mode
- Executing the planned ‘inter-epidemic’ preparedness research activities according to the EC grant agreement

1. Clinical Research Preparation Mode
- Assessing operational readiness in the networks, identifying important knowledge and resource gaps and preparing clinical protocols.

2. Clinical Research Mobilisation Mode
- Planning and implementing preparatory work necessary to achieve operational readiness in the networks to initiate a clinical research response to specific ID outbreak if and when needed.

3. Clinical Research Response Mode
- Implementing clinical research projects in the networks tailored to the specific ID outbreak, and addressing the most important and urgent clinical research questions.

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Overview of PREPARE’s process from receipt of trigger to delivery of a clinical research response to a (re-)emerging ID outbreak

**Outbreak Response Mode (ORM) assessment & decision**

- **a1** Trigger validation
- **a2** ORM assessment & advice by Outbreak Mode Committee (OMC)
- **a3** OR
  1. Informing General Assembly (GA) and European Commission (EC)
  2. GA consultation and decision
  3. Informing European Commission

**Development of Outbreak Response Plan (ORP)**

- **b1** Forming of Outbreak Response Team (ORT)
- **b2** Development of ORP
  1. Informing General Assembly (GA) and European Commission (EC)
  2. GA consultation and decision
  3. Informing European Commission

**Implementation of ORP**

- **c1** Execution of ORP tasks & progress monitoring
- **c2** OR
  1. Informing General Assembly (GA) and European Commission (EC)
  2. GA consultation and decision
  3. Amendment of EC Grant Agreement following standard procedures

**Continuous reassessment of outbreak situation by OMC and ORP**

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<table>
<thead>
<tr>
<th>Date</th>
<th>Outbreak</th>
<th>Trigger</th>
<th>Threat to Europe*</th>
<th>Mode</th>
<th>Activities</th>
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<td>28/04/2014</td>
<td>MERS-CoV</td>
<td>PREPARE partner</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Develop clinical protocols (collaboration with ISARIC).</td>
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<td>08/08/2014</td>
<td>Ebola Virus</td>
<td>PREPARE partner</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Surveyed PREPARE affiliated European hospitals to assess Ebola preparedness and capacity; Develop clinical protocols (collaboration with ISARIC).</td>
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<td>09/09/2014</td>
<td>Enterovirus 68</td>
<td>PREPARE partner</td>
<td>Low</td>
<td>Mode 0</td>
<td>No action. (WP3 MERMAIDS-PEDS study under development and would be ready to respond (in infants) once clinical sites activated).</td>
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<tr>
<td>04/12/2015</td>
<td>Zika</td>
<td>PREPARE partner</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Adapted WP3 CRFs and developed maternal and neonatal CRFs (in collaboration with ISARIC)</td>
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<tr>
<td>15/09/2017</td>
<td>CHIV</td>
<td>PREPARE partner</td>
<td>Low</td>
<td>Mode 0</td>
<td>No action. (Current WP3 MERMAIDS-ARBO study ready to respond in active sites).</td>
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<tr>
<td>11/01/2018</td>
<td>Influenza A H3N2</td>
<td>PREPARE Core Group</td>
<td>Limited</td>
<td>Mode 1</td>
<td>Assessment of operational readiness in PREPARE clinical WPs; communication brief outlining PREPARE position to address anxiety generated from media reporting.</td>
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* Threat determined by PREPARE OMC in response assessment
Real chikungunya virus (CHIV) scenario: timeframes for deciding on an Outbreak Research Mode.

15/09/2017 Trigger received from EVD Lab-net coordinator regarding a rising number of cases of autochthonous chikungunya virus (CHIV) in 3 European regions: Var, France; Lazio, Italy; Anzio, Italy (source: ECDC).

15/09/2017: Trigger validated, OMC met to initiate response assessment
ECDC risk assessment reviewed. No information on sequence comparison of virus was available. OMC agreed actions to progress response assessment.

9/10/2017: Response assessment complete: Mode 0 maintained.
Rationale for Mode 0: Emerging data confirmed that the CHIV outbreaks were of different strains. Further, the outbreaks were being brought under control with cases declining and seasonal activity of mosquitos (CHIKV vector) was in decline. It was considered unlikely that these outbreaks might signal potential for re-emergence the following year: a viremic traveller in a region with competent mosquitos typically introduces CHIV into that region and there is no primary animal reservoir in Europe.

11/10/2017: Outcome communicated with relevant stakeholders.
2. COMBACTE:

Clinical research on antimicrobial resistance
Pursuing Novel Antibacterials: New Drugs for Bad Bugs (ND4BB)

COMBACTE: Combatting Antibiotoc Resistance in Europe
COMBACTE: Combatting Bacterial Resistance in Europe

Four consortia:

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 pharmaceutical companies
The four pillars of COMBACTE

**CLIN-Net**
Clinical investigator network
Improve the efficiency of clinical study execution

**LAB-Net**
Laboratory surveillance network
Optimize diagnostics in clinical studies

**STAT-Net**
Improvements in trial design
Develop more efficient study designs & better methods for data analysis

**EPI-NET**
Epidemiology support for ND4BB & beyond
Improve information on AMR in Europe from existing surveillance systems
LAB-Net Network

- 762 routine diagnostic labs
- 1133 lab contacts
- 14 research labs
- 41 European countries

Distribution of the number of laboratories in LAB-Net per region in Europe as per WHO definitions

*As of November 2019
LAB-Net Goes Global

- 327 labs in 32 non-European countries

Overview of non-European laboratories collaborating with the LAB-Net network

GLOBAL STUDIES
CREDIBLE-CR
NeoAMR
PediCAP

*As of November 2019
Study specific activities (COMBACTE-NET and beyond)

- LAB-Net is involved in multiple studies and actively participates in all aspects of these studies

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<th>QoR selection</th>
<th>Dx test selection</th>
<th>Questionnaire</th>
<th>Site selection</th>
<th>Local lab Manual</th>
<th>Sample kits and study materials</th>
<th>Local lab training</th>
<th>EQA panel</th>
<th>Biobanking</th>
<th>Central Lab</th>
<th>Research lab</th>
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LAB-Net biobanking infrastructure

Central hub
UZA

-80°C freezers
-180°C automated system

LAB-Net
Decentralised Hub

Central LIMS system
LAB-Net biobanking data flow
concept developed for EXPECT-2 study
## COMBACTE, PREPARE and other Clinical studies

### COMBACTE NET

<table>
<thead>
<tr>
<th>Study name</th>
<th>Sponsor</th>
<th>Patients</th>
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### Shionogi

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**Recruitment status and numbers:**
- **ASPIRE-SSI:** 4946/5000, recruitment completed
- **WP6E tbd:** 72/600, recruitment completed
- **ARTHR-IS:** 750/240, recruitment completed
- **EXPECT 1:** 2006/2000, recruitment completed
- **EXPECTED 2:** 213, recruitment completed
- **WP7B:** 1007, recruitment completed
- **HONEST-PREPS:** 300, recruitment completed
- **ASPIRE-ICU:** 2266, recruitment completed
- **SAATELLITE:** 40, recruitment completed
- **ANTICIPATE:** 1013, recruitment completed
- **RESCUING:** 3163, recruitment completed
- **EVADE:** 184/285, recruitment completed
- **WP4B:** 220, recruitment completed
- **WP6G:** 225, recruitment completed
- **WP6H:** 1013, recruitment completed
- **MERMAIDS:** 831/1500, recruitment completed
- **MERMAIDS:** 1525, recruitment completed
- **REMAPP-CAP:** 644/800, recruitment completed
- **CREDIBLE-CR:** 121/150, recruitment completed
- **RESTORE-1M12:** 597/536, recruitment completed
- **CoBastin:** 288/343, recruitment completed
- **BAC0006:** 781/800, recruitment completed
- **AtoxBio:** 990, recruitment completed
- **Merck:** 1005, recruitment completed

**Total patients enrolled:** 20,062
European Clinical Trial Networks

Primary care + Hospital care + Labs + Pediatric care + Long Term Care

Primary care
>200 primary care practices in >20 European countries
- Recruited over 20,000 patients into clinical studies on ARTI
- Randomised 3,268 participants in a response-adaptive platform trial of a drug for a CA-ARTI

Hospital care + Labs
>850 hospitals and >750 labs in >40 European countries
- To date, this network is managing 19 trials, including phase I – III trials for 6 new compounds against multi-resistant bacteria, and recruited over 14,000 patients.

Pediatric care
90 paediatric clinical sites in 18 countries
- Active a.o in ZIKACTION, PREPARE, C4C (IMI2)

Long Term Care
Nursing homes and rehabilitation centres in 11 countries in Europe and Israel with more than 14,000 LTCF beds
- Experience in clinical trials on antibiotic use, influenza epidemiology and vaccines, microbiome and more.

Chris Butler
Marc Bonten (Clin)
Herman Goossens (Lab)

Carlo Giaquinto

Evelina Tacconelli
Mical Paul
3. ECRAID: European Clinical Research Alliance on Infectious Diseases
Leveraging EU/IMI investments in clinical research on AMR and EID

- Fast completion of clinical studies;
- Focus on bacterial infections and antibiotic resistance

Antimicrobial resistance

- Similar EARL barriers
- Overlapping stakeholders
- Shared need for adequately trained and staffed clinical study sites across Europe

Hence, need for a sustainable, operational high quality large-scale European Clinical Research Alliance for Infectious Diseases: ECRAID

Emerging Infectious Diseases

- Rapid initiation and completion of clinical studies;
- Focus on viral infections

ECRAID - Plan is funded by the European Commission under Grant Agreement 825715

3 Million EURO

Direct involvement of relevant other EU funded projects, networks and organisations

ECRAID-Plan is funded by the European Commission under Grant Agreement 825715
Overall goal:
Developing the detailed business plan for ECRAID, building on the high-level design developed in 2016 by the ECRAID Working Group

I. To **develop the detailed business plan** for ECRAID, based on COMBACTE and PREPARE.

   The ECRAID Business Plan will serve three main purposes:
   - Function as the central guiding document presenting the agreed strategy for the development of ECRAID;
   - Serve as a means to build awareness of and support for ECRAID amongst stakeholders;
   - Attract sufficient start-up funding/income to commence operations in ECRAID.

II. To **align** the ECRAID business plan to the activities, roles, mandates and ambitions of relevant other initiatives and organisations active in clinical research or complementary research on ID.

III. To **build awareness of and create support for** the ECRAID initiative amongst the broader group of stakeholders.
“We expect the ECRAID-Plan to come up with a business plan that offers concrete solutions and prepares Europe to better deal with antimicrobial resistance and large infectious diseases outbreaks”
– EU commissioner Carlos Moedas,

“an inspiring vision of a pan-European infrastructure for patients and communities, bringing public health, clinical and laboratory, science, innovation and society together.” – Sir Jeremy Farrar.

ECRAID-Plan is funded by the European Commission under Grant Agreement 825715
ECRAID-Plan

Coordination Team, UMCU

Herman Goossens
Marc Bonten

Project Support Office

Frank Deege, UMC Utrecht
Overall Business Plan (WP7)
WP rapporteur WPs 1, 2, 5 and 7

Nina Gobat, UOXF
Outbreak Response plan (WP7)
WP rapporteur WP3 Services and WP4 Operations

Melanie Hoste and Daniele Pazzola, UA
Communication plan (WP8)

Nicole van Erp, UMC Utrecht
Project management (WP9)

Herman Goossens
Marc Bonten

Coordination Team, UMCU

Frank Deege, UMC Utrecht
Overall Business Plan (WP7)
WP rapporteur WPs 1, 2, 5 and 7

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Nicole van Erp, UMC Utrecht
Project management (WP9)

Sam Sluismans
Project Partner

Pieter Sauwens
Project Manager

Naomi Opsomer
Project team

Monitor Deloitte

Anne Massij
Life sciences & healthcare expert

Edith Maes
Healthcare expert

Eliana Biundo
Life sciences & health policy expert

Burçak Aydin
Clinical outcomes research expert

Elias Van Herwaarden
Location strategy expert

Lyn Venken
R&D tax incentives and grants expert

Roman Lopez
R&D tax incentives expert
4. VALUE-Dx:

Setting the scene for public-private collaborations in diagnostics of infectious diseases
VALUE-Dx

Setting the scene for public-private collaborations in diagnostics of infectious diseases
Objectives of VALUE-Dx

Helping to build the economic case for rapid diagnostics as a public good in the fight against AMR

1. To **design a health-economic framework (HEF)** to assess and demonstrate the value of diagnostics both for individual patients and for public health impact by reducing antibiotic use and subsequent antibiotic resistance among patients.

2. To **establish a sustainable European Standardised Care Network** adequately trained and resourced to conduct clinical trials evaluating the value of diagnostics.

3. To **design and implement clinical studies to demonstrate the value of diagnostics** in the optimal management of Community-Acquired Acute Respiratory Tract Infections (CA-ARTIs)

4. To **explore, define and attempt to resolve the psychological, ethical and social barriers** which prevent the more widespread adoption of diagnostics delivering healthcare to the population.
The VALUE-Dx Consortium
Interaction between the Work Packages

1. Technological and Clinical value factors
   - Data on CA-ARTI-Dx accuracy to feed economic models
   - WP5 EAP input
   - Health-economics input
   - Data from PPAS and Clinical trial ESCAN input, Data from Task 4.4

2. Lab. analyses & biobanking
   - Microbiology input
   - CA versions
   - Bio-banking

3. Data-management and analytics
   - Clinical data
   - PPAS tool, eCRFs, repository
   - Datamanagement and repository

4. Clinical Study
   - Samples

5. Economic value, policies and funding models
   - Health-economics data

6. Education and Advocacy
   - Comm. Support
   - VALUE-Dx Course
   - contents for dissemination, communication and training actions

7. Project Management & Sustainability
   - Progress reports
   - Mgt support VALUE-Dx EAP
   - Business Plan
# PROJECT TIMELINE & STATUS UPDATE

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- Work in progress -

- Deloitte to take lead  - Deloitte to join

Together with ECRAID: present coherent overall Business Plan
Integration of sustainability plans of ECRAID-Plan and VALUE-Dx

ECRAID-plan sustainability plan

✓ Building infrastructure for clinical trials of Infectious Diseases in all clinical care settings

VALUE-Dx sustainability plan

✓ Building infrastructure for clinical trials and labs on diagnostics of Infectious Diseases
✓ Building biobank
✓ Building database
What ECRAID could offer

- Clinical Trial Network for infectious diseases in hospital care and primary care, adults and children
- Rapid access to target European patient populations
- Globally embedded
- Single-point of access into a high quality, business oriented clinical research network
- Focus on services that alleviate the Ethical, Administrative, Regulatory and Logistical (EARL) barriers to clinical research (faster start-up, reduce timelines, lower costs)
- Direct access to leading expertise on Infectious Diseases
- An active network, continuously including patients in platform trials, allowing rapid clinical research response in the event of an EID or pandemic threat

ECRAID-Plan is funded by the European Commission under Grant Agreement 825715
ECRAID: Our plan and timelines

Detailed Design of Business plan and operating model

High level Design completed

Construct & Implement

FUNDING THROUGH IMI2 FOR Dx PART (VALUE-Dx – 1.4.2019 – 31.3.2023))

FUNDING through H2020 (call – 8 April 2020)

FUNDING through public and private partnerships

FUNDING THROUGH H2020 project (ECRAID-Plan 1.1.2019 – 31-12-2020 and VALUE-Dx)

High level Design

PREPARE

end of current funding

COMBACTE-Net

end of current funding

CURRENT THINKING FOR A NEW H2020 PROPOSAL: A SINGLE-ACCESS CLINICAL RESEARCH NETWORK FOR PREPAREDNESS AND RESPONSE TO INFECTIOUS DISEASES OUTBREAKS, REDUCING THE IMPACT OF INFECTIOUS DISEASES ON INDIVIDUAL AND POPULATION HEALTH

Legend: HAP = Hospital Acquired Pneumonia; VAP = Ventilator Associated Pneumonia; IAbd – Intra-Abdominal diseases; CAP = Community Acquired Pneumonia; CA-ARTI = Community Acquired Respiratory Tract Infections; cUTI – Complicated Urinary Tract Infections; ARBO-ID = Arthropod-Borne Infectious Diseases
Thank you