



Innovative Medicines Initiative

New Drugs 4 Bad Bugs (ND4BB)

Topic 5 : Clinical Development of antibacterial agents for Gram-negative antibiotic resistant pathogens

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Antibiotic-resistant infections spread through Europe

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

cial returns are low. The European Commission yesterday launched a plan to boost research into new antibiotics, by promising accelerated approval for new drugs and funding for development through the the Innovative Medicines Initiative, a public-private collaboration with the pharmaceutical industry.

Three million Europeans catch infections in hospital annually

G8 debating antibiotic resistance

Antibiotic resistance: we must act now, says WHO

THE  **TIMES**

13:56 17Nov11 RTRS-UPDATE 1-Europe kickstarts R&D fightback against superbugs

- * Need to combat antibiotic resistance now "critical"
- * EU to accelerate new drug approvals, ensure adequate pricing
- * Plan to boost R&D collaboration via IMI initiative
- * Drugmakers welcome fresh incentives for antibiotic research



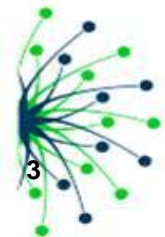
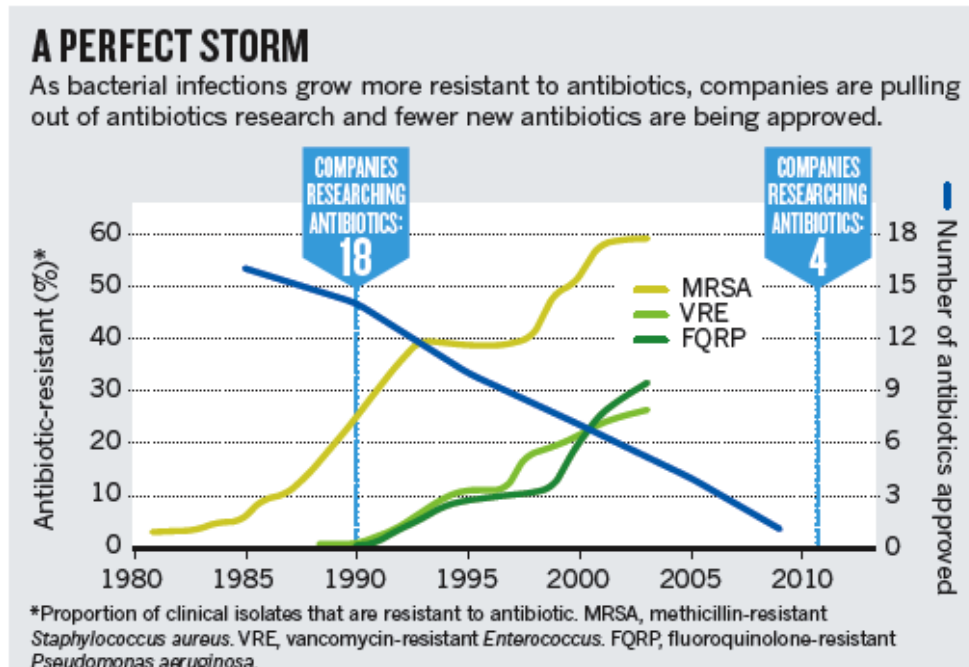
ND4BB: Need for public-private collaboration



- The overall vision of ND4BB is to create an innovative collaborative Public-Private Partnership (PPP)-based approach that will encompass all aspects from the discovery of new antibiotics to Phase 2 and 3 clinical trials with the aim of reinvigorating antibiotic R&D

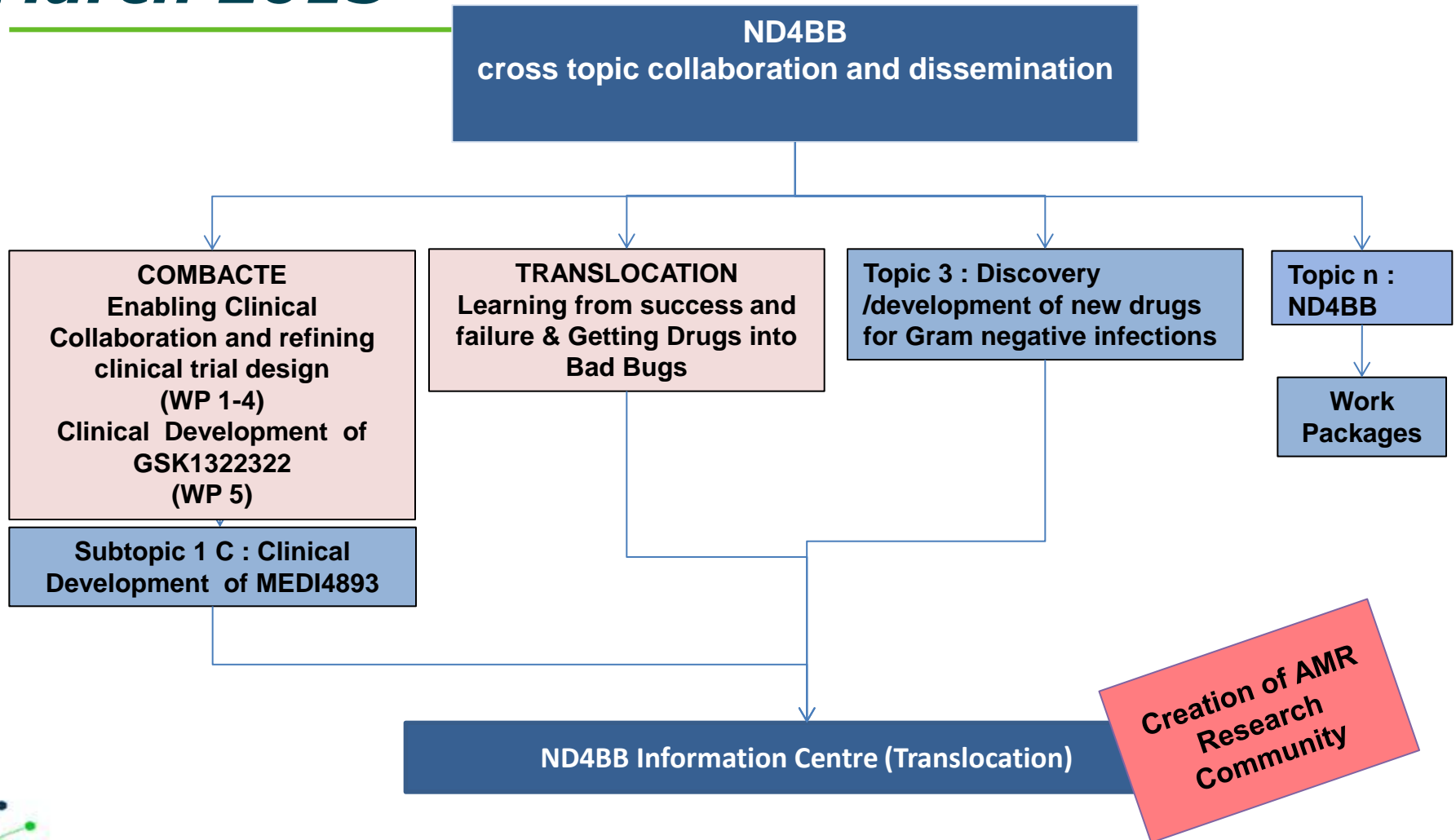
Three key challenges in antibiotic R&D:

- Discovery:** Unique scientific bottlenecks
- Development:** Challenging regulatory environment
- Economics:** Low return on investment



ND4BB Overall Structure

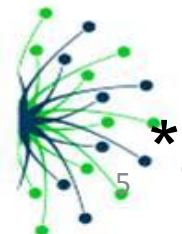
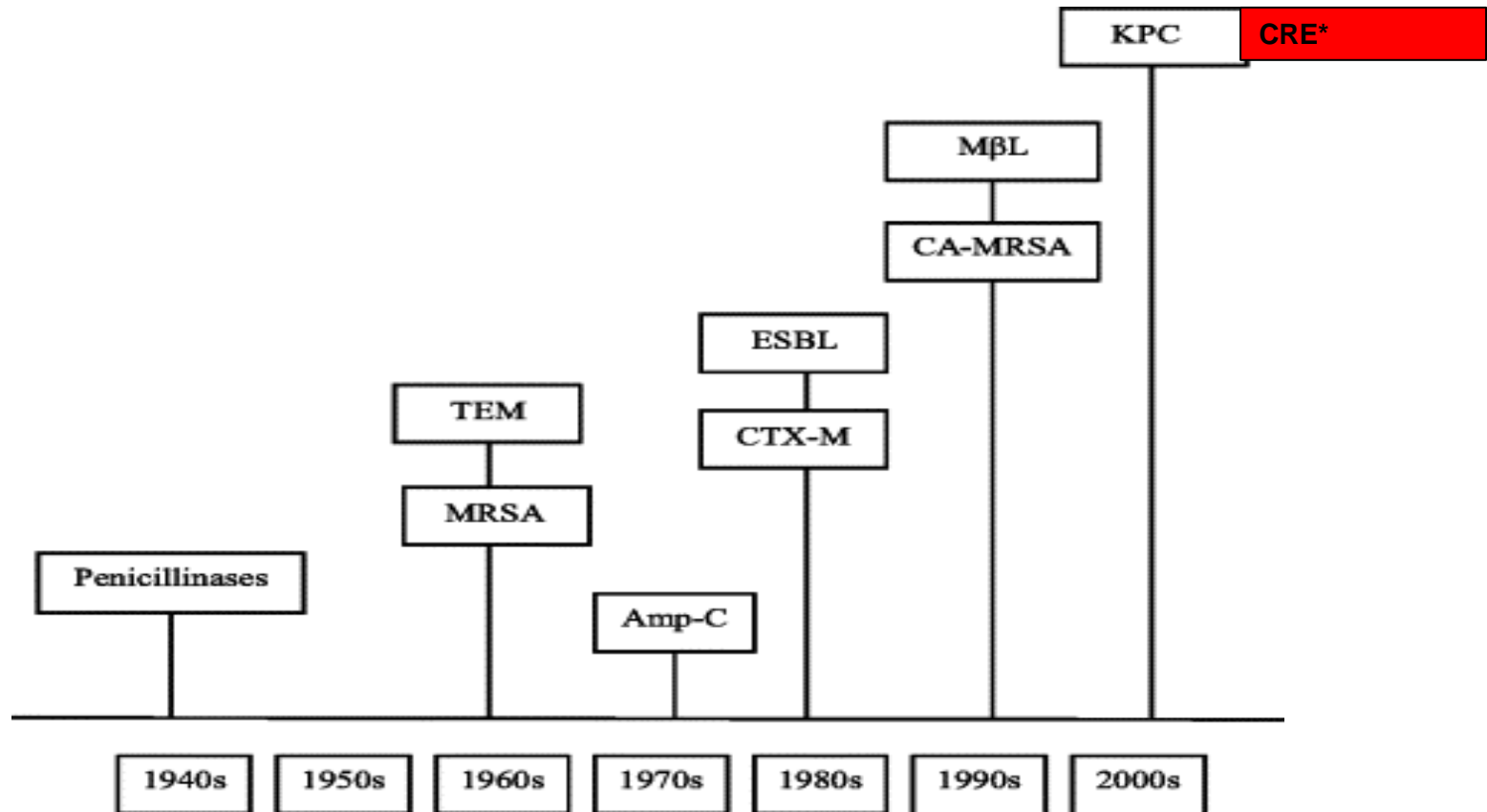
March 2013



- Topics launched under Call 6 (July 2012)
- Topics launched under Call 8 (December 2012)



Antibiotic resistance is unpredictable



*

CRE – Carbapenem resistant enterobacteriaceae



Antibiotic resistance

- Sporadic and heterogeneous



Figure 4.13: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with combined resistance (resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides), by country, EU/EEA countries, 2011

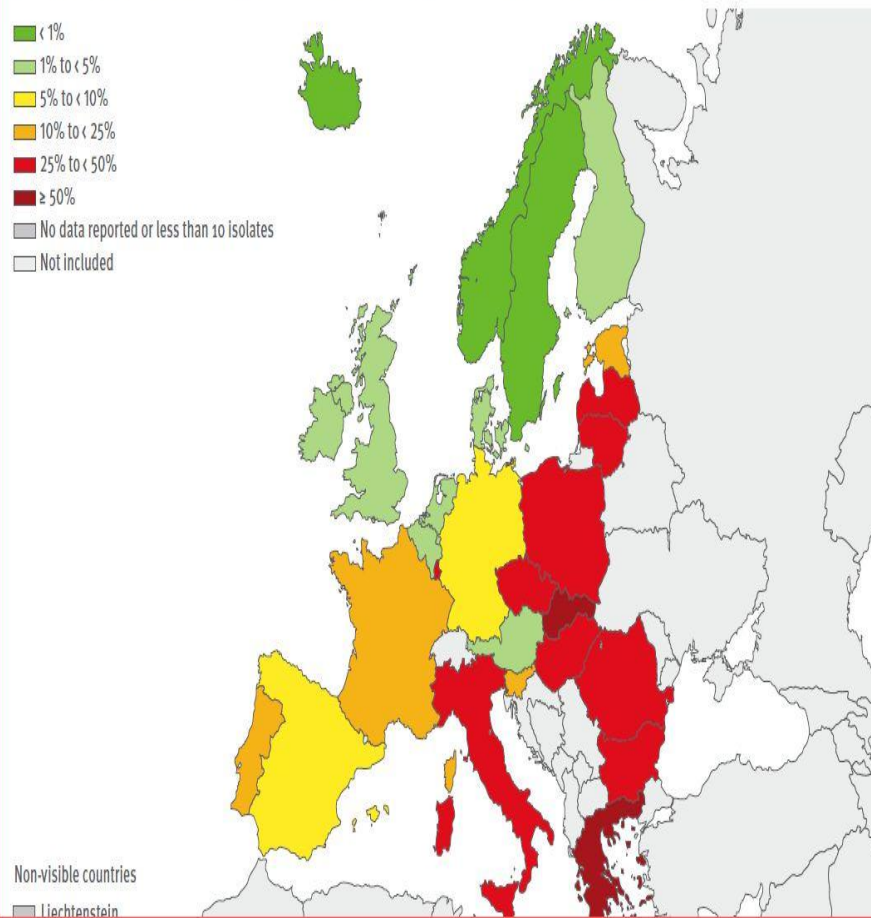
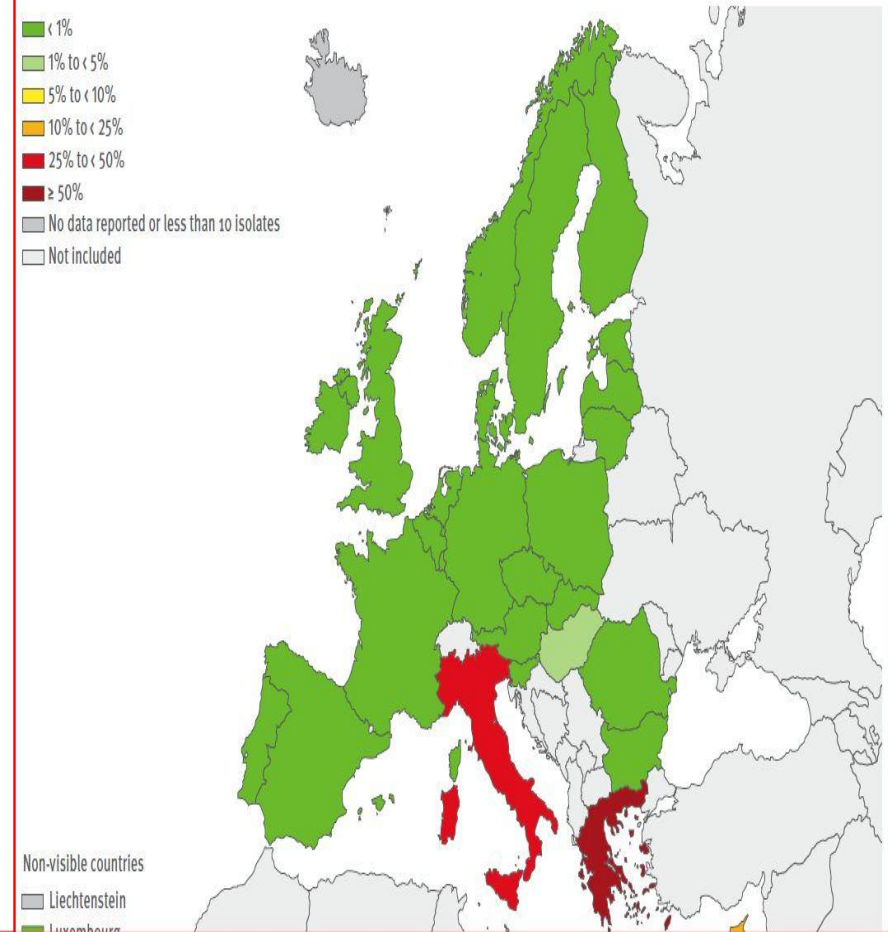


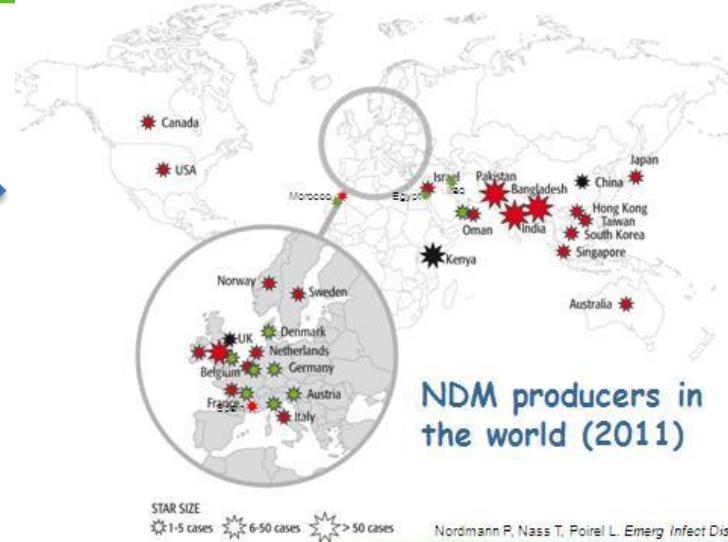
Figure 4.12: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2011



Antibiotic resistance is unpredictable



Environmental sites of NDM-1 producers (Delhi)



- NDM spread to ICUs across Europe in <18 months
- Numerous examples of rapid global spread of clones & resistances
- Takes 10+ years to make an AB
- Long term strategy needed for threats of today and the future



— Nordmann et al (2011); Emerging InfectDis 17; 1791-8.
 Klugman (2002); J. Antimicrob Chemother, 50; S2, 1-5.
 Walsh et al (2011); Lancet, 11,(5) , 355- 362



Antibiotic development pathways

Existing regulatory framework defines the spectrum



Traditional Development:

Two well-controlled, adequately powered Phase III studies per body site to demonstrate safety and efficacy

Focused on
body sites of
infection

A large, light blue circle with a dark blue gradient border, containing the text 'Pathogen-focused development as a middle path'. A horizontal black line with circular end caps passes behind the circle.

**Pathogen-
focused
development as a
middle path**

The Animal Rule:

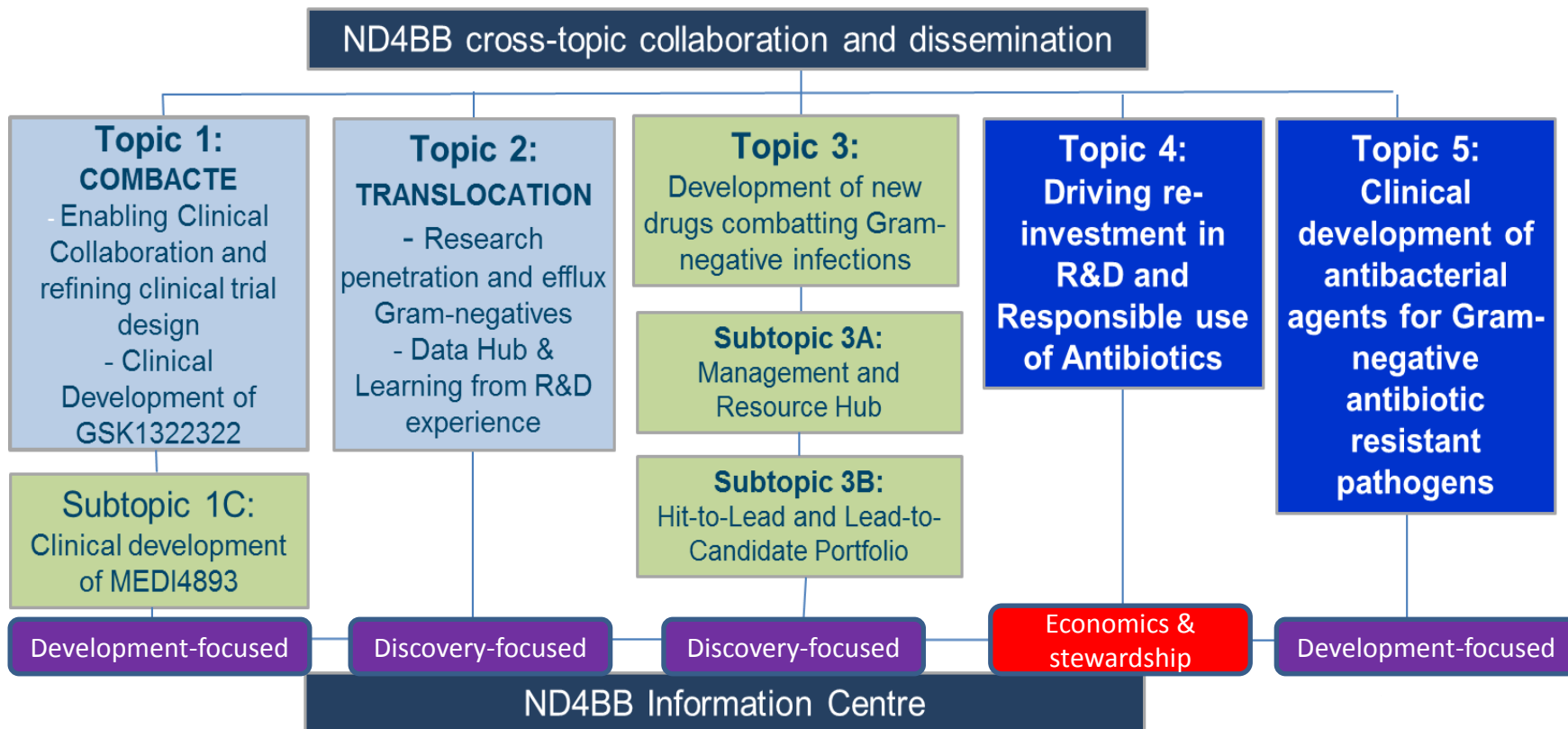
For cases when studies in humans are unethical; Approval based on human safety studies and preclinical (non-human) efficacy studies

Focused on
infectious agent



ND4BB Overall Structure

July 2013



- Projects from Call 6 initiated 1/01/2013
- Topics launched under Call 8 (Dec 2012)
- Topics launched under Call 9 (July 2013)



Call 9, Topic 5 - Clinical Development of antibacterial agents for Gram-negative antibiotic resistant pathogens



OVERALL OBJECTIVES

- Increase the efficiency of antibiotic R&D through analysing observational clinical and microbiological data sets and making recommendations for the development of novel antibiotic agents for MDR Gram-negative pathogens
- Understand the clinical management and outcomes of patients with serious hospitalised infections to validate our understanding of the clinical outcomes for patients in areas of emerging and endemic antibiotic resistance.
- Support the sustainability of ND4BB supported investigator and laboratory networks.
- Conduct prospective clinical trials with novel trial designs to deliver safety, pharmacology, and proof of efficacy data for a novel agents/combinations, in particular aztreonam-avibactam (ATM-AVI) directed towards treatment of infections due to priority pathogens.



Call 9, Topic 5 - Clinical Development of antibacterial agents for Gram-negative antibiotic resistant pathogens



EXPECTED DELIVERABLES

- Successful phase 1, phase 2 and/or phase 3 clinical trials demonstrating the pharmacology, safety and efficacy of new antibiotics against priority pathogens.
- Observational clinical and microbiological data relevant to the future development and use of new and existing products.
- Working with existing ND4BB consortia to support the build of a functioning investigator network for the conduct of antibacterial clinical trials and non-interventional trials in European geographic areas with high levels of resistance



Call 9, Topic 5 - Clinical Development of antibacterial agents for Gram-negative antibiotic resistant pathogens



PART A – Conduct of observational clinical research to inform the design, conduct and interpretation of development programmes for antibacterial agents targeted MDR gram-negative bacteria.

PART B - Conduct of Clinical therapeutic studies to support the development of Aztreonam-Avibactam (ATM-AVI)

Intended applicant consortia are expected to apply for both PART A and PART B



PART A – Conduct of observational clinical research to inform the design, conduct and interpretation of development programmes for antibacterial agents targeted MDR gram-negative bacteria.



Key objectives

- Increase the efficiency of antibiotic R&D through analysing observational and microbiological data sets reflecting a “real-world” population and making recommendations for the development of antibacterial agents for MDR Gram-negative pathogens
- Understand the routine clinical management and characterize the spectrum of outcomes of patients with serious hospitalised infections to validate our understanding of patient outcomes in areas of endemic and emerging antibiotic resistance
- Support the sustainability of ND4BB supported investigator and laboratory networks



PART A – Conduct of observational clinical research to inform the design, conduct and interpretation of development programmes for antibacterial agents targeted MDR gram-negative bacteria.



Workpackage outline

- WP1: Retrospective observational study to assess the clinical management and outcomes of patients with hospitalized complicated intra-abdominal infection or nosocomial pneumonia in areas of endemic and emerging Gram-negative multi-antibiotic resistance.
- WP2: Prospective observational study to assess the clinical management and outcomes of patients with serious hospitalized infections known or suspected to be caused by MDR Gram-negative bacteria.
- WP3: Programme management, collaboration with the other ND4BB projects and dissemination



WP1 :Retrospective observational study to assess the clinical management and outcomes of patients with hospitalized complicated intra-abdominal infection or nosocomial pneumonia (NP) in areas of endemic and emerging Gram-negative multi-antibiotic resistance



Objectives

- To provide accurate clinical and microbiological data in patients with NP and complicated intra-abdominal infections (cIAI) in the selected countries
- To evaluate and quantify patient and disease characteristics, treatment options and clinical outcomes.

Design, Population, and Setting

- Retrospective cohort, hospitalised patients with NP and cIAI diagnosed 2-year prior to study start
- 6-12 month period in approx 1000 patients from at least 6 countries (including Greece, Turkey, Italy, Spain, Bulgaria, Serbia, Croatia and Romania)
- Diagnosis of NP and cIAI will be determined by chart review and electronic records based on pre-agreed ICD-9 codes or similar methodologies



WP2: Prospective observational study to assess the clinical management and outcomes of patients with serious hospitalized infections known or suspected to be caused by MDR Gram-negative bacteria.



Objectives

- To provide accurate clinical and microbiological data for hospitalised patients with infections known or suspected to be caused by selected antibiotic resistant Gram-negative pathogens with the aim of
 - Understanding clinical outcomes in relation to underlying resistance mechanisms across cIAI, NP and nosocomial blood-stream infections (BSI)
 - Evaluating the efficacy and tolerability of best available therapy for cIAI, NP and BSI due to selected antibiotic resistant bacteria

Design, Population, and Setting

- Observational prospective cohort study of hospitalised patients presenting with either cIAI, NP or nosocomial BSI known or suspected to be caused by either;
 - a) Carbapenem resistant Enterobacteriaceae and/or
 - b) Carbapenem resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- 2-year duration with approx 1000 patients from at least 6 countries (including Greece, Turkey, Italy, Spain, Bulgaria, Serbia, Croatia and Romania) with 5-10 centres per country



WP3: Programme management



Objectives

- To ensure effective programme management and co-ordination across all of the Topic 5 workpackages
- Ensure collaboration across Topic 5 investigators
- Strategic alignment and collaboration with COMBACTE and across other ND4BB projects
- Promote alignment with other AMR research collaborations
- Sharing and dissemination of data/results through the ND4BB Information centre and the wider scientific community



Topic 5, PART B – Conduct of clinical therapeutic studies to support the development of Aztreonam-Avibactam (ATM-AVI)



Key objectives

- Conduct prospective clinical trials with novel trial designs to deliver safety, pharmacology and proof of efficacy data for a novel β -lactam/ β -lactamase inhibitor combination directed towards treatment, prevention, or sequelae of infections due to priority pathogens and if possible to validate novel bacterial identification diagnostics or clinical endpoints with the aim of reducing the size and cost of future clinical trials



ATM-AVI (1)



- The incidence of serious infections due to MDR in Gram-negative pathogens is increasing.
- Mainly driven by the increasing prevalence and complexity of a variety of β -lactamases, the most important of which are the extended spectrum β -lactamases (ESBLs) and carbapenemases, including *Klebsiella pneumoniae* carbapenemase (KPC).
- Within the carbapenemases, a growing threat is posed by the metallo- β -lactamases (MBLs), including the recently emerging New Delhi metallo- β -lactamase (NDM-1). The latter is a particular concern because the genetic element encoding NDM-1 is able to rapidly spread amongst bacteria in both community and hospital settings.
- Aztreonam, with more than 25 years of use worldwide, is an established injectable antibiotic indicated for the treatment of various infections caused by susceptible Gram-negative bacteria. It has a unique monocyclic β -lactam nucleus, that makes it structurally different from other β -lactam antibiotics (including penicillins and cephalosporins), as well as several chemical side groups that interfere with degradation by MBLs.
- Therefore Aztreonam theoretically could retain activity against MBL (Class B) producing pathogens. However inactivation by co-produced Class A, C, or D β -lactamases remains problematic.



ATM-AVI (2)



- Avibactam is a non β -lactam, β -lactamase inhibitor of a broad spectrum of enzymes, including Ambler Class A ESBLs, Class A KPC, and Class C (AmpC) enzymes, and some Class D enzymes, notably OXA-48.
- Avibactam's β -lactamase inhibition occurs through formation of a covalent bond between avibactam and enzyme. Alone, avibactam has no meaningful antibacterial activity; rather, its beneficial effect in combination with aztreonam occurs by rendering inactive those enzymes that inactivate aztreonam.
- Together, aztreonam and avibactam have the potential to address the unmet need for safe and effective agents to combat MBL-producing MDR organisms.
- Phase 1 safety and PK study of ATM-AVI is ongoing (UK).



PART B – Conduct of clinical therapeutic studies to support the development of Aztreonam-Avibactam (ATM-AVI).



Workpackage outline

- WP4: Phase IIa pharmacokinetic/pharmacodynamic analysis of ATM-AVI in patients with serious infections caused by Gram-negative pathogens.
- WP5: Phase III randomised, multicenter, clinical study to evaluate the efficacy and safety of ATM-AVI in the treatment of serious infections caused by Gram-negative pathogens proven or strongly suspected to be caused by multi-drug resistant pathogens including metallo- β -lactamase producers.
- WP6: Management of ATM-AVI Clinical programme and integration with overall Topic 5 and ND4BB programme



WP4: Phase IIa pharmacokinetic/pharmacodynamic analysis of ATM-AVI in patients with serious infections caused by Gram-negative pathogens.



Key Study Objectives

- To determine the safety, tolerability and pharmacokinetics of ATM-AVI versus meropenem for the treatment of complicated intra-abdominal infections and nosocomial pneumonia in hospitalized adult patients
- Investigate the PK of ATM-AVI in a patient population similar to the target population and support extensive modelling assessments

Design, Population, and Setting

- Study will randomize approximately 75 patients in a 2:1 ratio (ATM-AVI: meropenem)
- Included patients will be those hospitalized adults with a diagnosis of cIAI or HAP/VAP
- EU sites



WP5: A Phase 3 study to evaluate the efficacy, safety and tolerability of aztreonam-avibactam for the treatment of serious infections proven or highly suspected to be due to metallo- β -lactamase producing Gram-negative pathogens



Key Study Objectives

- To evaluate the efficacy of, and microbiological response to, ATM-AVI compared to meropenem-colistin (MER-COL) at test of cure (TOC) for the treatment of selected serious infections that are proven or strongly suspected of being due to MBL-producing bacteria
- To evaluate the PK of ATM-AVI and to characterize the relationship between exposure and clinical and microbiological response
- To evaluate the safety and tolerability profile of ATM-AVI compared to MER-COL.

Design, Population, and Setting

- Prospective, randomized, multicentre, assessor-blind, parallel group, comparative
- Approximately 400 patients globally, will be randomised in countries that have reported the emergence of MBL-producing Gram-negative pathogens (e.g. India, Greece, Russia)
- Current data suggests that there could be approximately 125 patients recruited with Europe
- Included patients will be those hospitalized adults with cIAI or HAP/VAP and where the index of clinical suspicion for an infection with an MBL-producing Gram-negative organism is high (prior antibiotic use, long duration of antecedent hospital care, comorbidities etc)
- The primary efficacy variable will be the proportion of patients with clinical cure at TOC (Day 25) in the modified intent to treat population which will comprise all randomized subjects who receive any amount of study drug.



WP6: Management of ATM-AVI Clinical programme and integration with overall Topic 5 and ND4BB programme



Objectives

The main purpose of this WP will be to ensure effective programme management of the ATM-AVI clinical programme within ND4BB, ensure collaboration with the overall Topic 5 programme and support WP3 in its alignment and collaboration with ND4BB consortia

- ensure effective coordination of the clinical trial operations and management across WP 4 and 5 and integration with the AstraZeneca project team
- collaborate with other partners outside Europe involved in the global development of ATM-AVI
- integrate with the overall Topic 5
- ensure adequate product and GCP training and qualifications of investigators within the Consortium conducting WP4 and WP 5.



Topic 5 : Expected contributions of the applicants*



- Networks, hospitals and healthcare institutions with capability to conduct observational and therapeutic clinical trials in both the indications of interest and in the identified geographic areas, eg,
 - Greece, Turkey, Italy, Spain, Bulgaria, Croatia, Serbia, Romania, UK
- Expertise in the conduct of GCP clinical studies in ICU / surgical / medical bacterial infections to participate in pan-European program
- Expertise in current standard of care for patients with cIAI, nosocomial pneumonia and nosocomial bloodstream infections in geographic areas on interest
- Expertise in observational study design and conduct to create protocols, determine relevant pathogens, antibacterial agents, clinical correlates and analyses.

*Selected examples, please refer to the call text for more details



Topic 5 : Expected contributions of the applicants*



- Clinical microbiology lab capability to address all relevant aspects of the protocols
- Project leadership and quality assurance, coordination infrastructure
- Data storage, processing, analysis and reporting capabilities
- Clinical or academic research organization with experience in P2 and P3 acute hospital care studies in geographic areas on interest.

*Selected examples, please refer to the call text for more details



Topic 5 : Expected(in-kind) contributions of EFPIA members



- Expertise in designing and conducting clinical trials
- Knowledge & expertise in antimicrobial R&D
 - Provision of study drug, regulatory support, project management, pharmacovigilance, clinical expertise, etc.
 - Support for clinical sites and labs to ensure they are “audit ready.”
- Non-European component of the clinical trials
- Project/alliance management personnel; workshops/seminars/Q&As
- Statistics, PK/PD modeling & simulation expertise
- Expertise in relation to clinical microbiology procedures/protocols required in clinical trials



Topic 5: Allocation of funding, milestone progression



- Call 9, ND4BB, Topic 5 to include indicative budgets on both PART A and PART B
- Applications being sought for the whole of Topic 5 (PARTs A and B)
- Decisions to conduct the PART B (WP4) in patient PK/PD analysis or to incorporate within WP5 will be taken as soon as external regulatory and expert opinion has been reviewed by the EFPIA sponsor
- WP5 is anticipated to start no sooner than 2H2014 with corresponding stepwise allocation in funding
 - Design of WP 5 is dependent on final agreed development plan with regulatory guidance, internal EFPIA sponsor governance and possibly results from the observational study (WP 1) and other EFPIA company sponsored surveillance and clinical research
- Consortium (including the sponsoring EFPIA partner) to determine the need for an Open Call to engage additional clinical sites/beneficiaries to conduct the clinical studies based on the updated study details



Questions?



- Contact the **IMI Executive Office**

E-mail: infodesk@imi.europa.eu

Website: www.imi.europa.eu

Potential applicants should not contact EFPIA personnel directly.

All questions should go through the IMI Executive Office

