



Innovative Medicines Initiative

Combating Antibiotic Resistance: New Drugs 4 Bad Bugs (ND4BB) Subtopic 1C

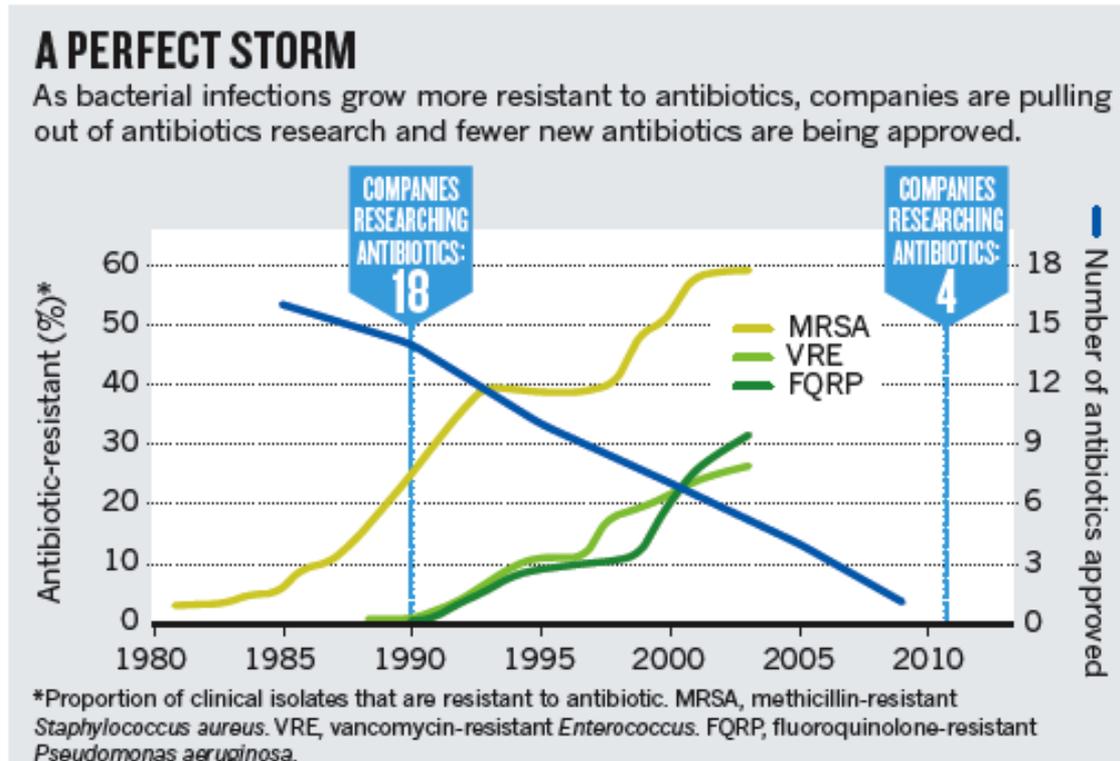
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Need for public-private collaboration



Challenges of AB R&D:

1. Unique scientific bottlenecks
2. Challenging regulatory environment
3. Low return on investment



Challenges too great for any single entity to solve, collaboration is essential



Objectives of the full project

- Response to the European Strategy to combat antibiotic resistance
 - Antimicrobials R&D PPPs have been the subject of years discussion; ND4BB establishes Europe as a leader in addressing AMR
- Information sharing amongst collaborators in a way we have never done before
 - Need to increase the overall success of antimicrobials R&D, as an industry we cannot afford to make the same mistakes twice
- Projects focused on the treatment/prevention/management of resistant infections caused by:
 - Drug-resistant Gram-negative pathogens
 - *Clostridium difficile*, methicillin-resistant *S. aureus* (MRSA)



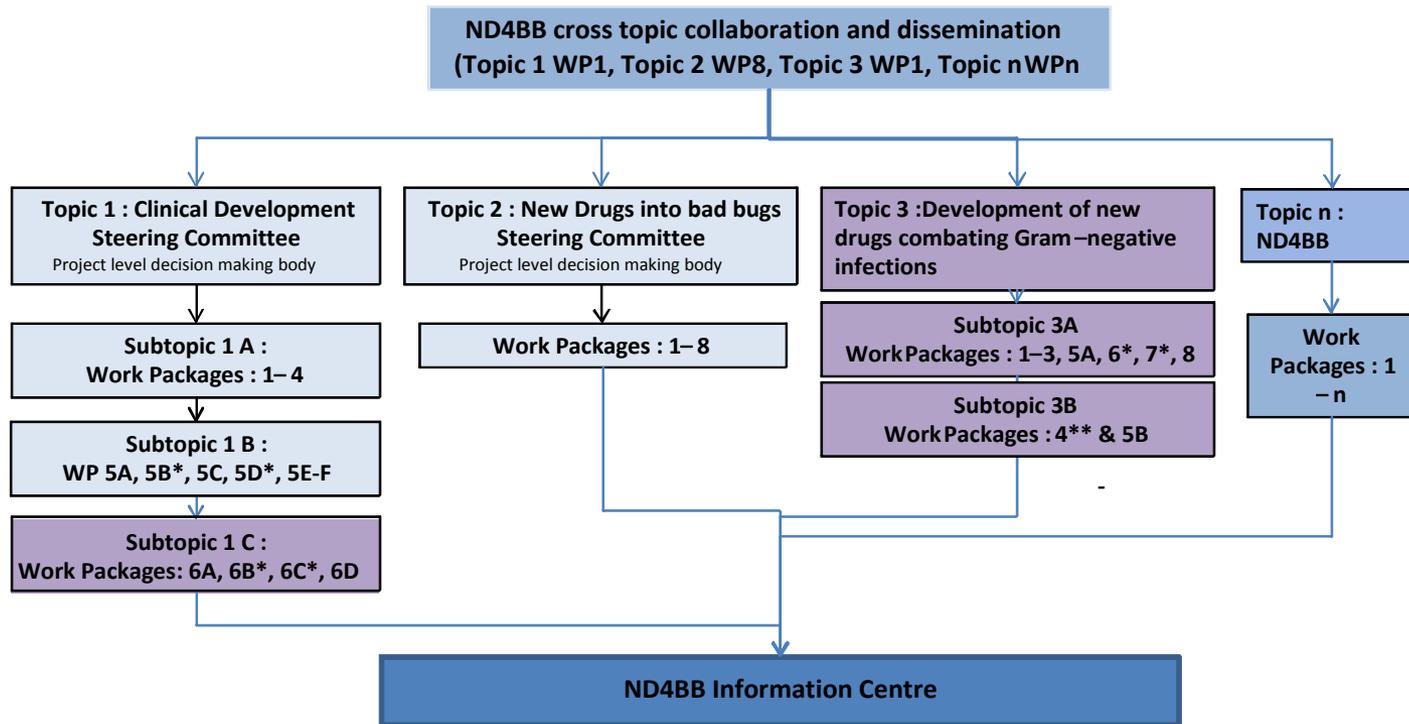
Expected impact on the R&D process



- Sharing of successes and failures amongst the industry will increase the efficiency of antimicrobials R&D
- Potential to create smaller & more efficient clinical trials
 - Biomarker research and rapid diagnostics could enable targeted patient enrolment
- Creation of a clinical trial consortium for antibacterials
 - Creation of more sites in areas of high resistance
 - Communication of best practice and learnings
- Ability to rationally design compounds that penetrate Gram-negatives will facilitate the delivery of a pipeline of antimicrobials for Gram-negatives



Suggested architecture of the project



- Topics launched under Call 6
- Topics to be launched under Call 8
- * Subject to milestones approval and potentially Call for additional beneficiaries
- ** Potentially subject to Call for additional beneficiaries if needed to provide additional Hit-to-Lead efforts
- Future Topics to be launched



Key deliverables of the full project: Topic 1



- *Challenge being addressed:* funding for antimicrobials clinical trials is a major cost of development (in some cases prohibitive)
- *Goals & deliverables:* Provide clinical data on new agents for tackling priority pathogens and improving the efficiency of antimicrobial clinical trials
 - Generation of clinical data that demonstrate the efficacy, safety, and pharmacology of new agents for priority pathogens
 - Create the first clinical trial consortium for antimicrobials
 - Create opportunities to test diagnostics/biomarkers, etc
 - Create new clinical trial sites in regions/institutions of high antimicrobial resistance
 - Innovative Phase 2 and Phase 3 designs



Current Call 8, Subtopic 1C, WP6: Development of MEDI4893, a monoclonal antibody targeting *S. aureus* alpha toxin



Objectives

- To evaluate the burden of *S. aureus*-related disease and identify potential target populations by establishing population-specific surveillance programmes to support the clinical development of MEDI4893
- To conduct prospective clinical studies to deliver safety, pharmacology, and proof of efficacy data for MEDI4893, a novel monoclonal antibody directed toward the prevention of *S. aureus* disease



Current Call 8, Subtopic 1C, WP6: Development of MEDI4893, a monoclonal antibody targeting *S. aureus* alpha toxin



- WP6A: Epidemiologic surveillance of healthcare-associated infections (HAIs) amongst surgical and intensive care unit patients in the European Union
- WP6B: Phase 1b/2a study with MEDI4893 for the prevention of *S. aureus* ventilator-associated pneumonia (VAP)
- WP6C: Phase 1b/2a study with MEDI4893 for the prevention of *S. aureus* surgical site infections (SSIs)
- WP6D: newly added WP to manage WP6A-6C activities including programme management, training, and integration with the overall Topic 1



- *S. aureus* produces tissue and organ damage in part via toxins
- Preemptive targeting of these toxins may prevent serious *S. aureus* (including MRSA) disease in high-risk patients, independent of the antimicrobial resistance status.
 - Alpha toxin (AT) is a cytolytic pore-forming toxin and a key virulence factor
 - Leads to tissue disruption, bacterial dissemination, and immune dysregulation
 - Mutant *S. aureus* strains lacking AT have reduced virulence in animal models
- MEDI4893 is a human IgG1 that potently neutralizes *S. aureus* AT
 - MEDI4893 prevents immune evasion, tissue damage
 - Prevents serious disease in animal models: lethal pneumonia, dermonecrosis, sepsis
- MEDI4893 is not expected to contribute to antibiotic resistance
- Phase 1 safety and PK study to be conducted in the U.S.



Subtopic 1C, WP6: Innovative Trial Design & Clinical Drug Development



WP6A: Epidemiologic surveillance of healthcare-associated infections (HAIs) among surgical and ICU patients in the EU

Objectives

- To estimate the incidence of and risk factors for *S. aureus* HAI, including surgical site infections (SSI) and ICU pneumonia
- To assess the prevalence of SSI and ICU pneumonia by etiologic agent and describe antimicrobial susceptibility patterns
- To explore the role of antibodies against Gram-positive and Gram-negative bacterial virulence factors as biomarkers of disease risk and outcome

Design, Population, and Setting

- Prospective, 24-month active surveillance in 10-20 hospital network hubs in 6-12 EU countries (2014-2016)
- Clinical and laboratory data on a minimum of 50,000 patients undergoing complicated surgeries and 5,000 patients admitted to the ICU
- Linked pre-exposure (i.e., pre-surgery or pre-ICU) serologic samples stored/collected
- Use of standardized case definition; lab confirmation of etiologic agent of infection
- Sites with demonstrated expertise in conduct of patient-based HAI surveillance



Subtopic 1C, WP6: Innovative Trial Design & Clinical Drug Development



WP6B: Ph 1b/2a trial for prevention of *S. aureus* (including MRSA) ventilator-associated pneumonia (VAP)

Key Study Objectives

- To evaluate the safety, tolerability, and pharmacokinetics (PK) of MEDI4893 administered to mechanically ventilated ICU patients
- To evaluate the effect of MEDI4893 on the incidence of *S. aureus* pneumonia in mechanically ventilated ICU patients
- To evaluate biomarkers associated with *S. aureus* disease severity and outcome

Design, Population, and Setting

- Randomized, double-blind, placebo-controlled; estimated sample size = 400; EU sites
- Subjects admitted to the ICU without pneumonia, deemed at increased risk of developing *S. aureus* (including MRSA) pneumonia, and who require mechanical ventilation
 - Individuals at high risk of *S. aureus* VAP are those with an expected risk of *S. aureus* VAP of $\geq 25\%$



Subtopic 1C, WP6: Innovative Trial Design & Clinical Drug Development



WP6C: Ph 1b/2a trial for prevention of *S. aureus* (including MRSA) surgical site infections (SSIs)

Key Study Objectives

- To evaluate the safety, tolerability, and pharmacokinetics (PK) of MEDI4893 administered to surgical patients at high risk for *S. aureus* SSI
- To evaluate the effect of MEDI4893 on the incidence of *S. aureus* SSI in surgical patients at high risk for *S. aureus* SSI
- To evaluate biomarkers associated with *S. aureus* disease severity and outcome

Design, Population, and Setting

- Randomized, double-blind, placebo-controlled; estimated sample size = 300; EU and global sites
- Surgical patients at high risk for developing *S. aureus* SSIs, with a recent history of *S. aureus* SSI
 - Expected *S. aureus* SSI rate of $\geq 20\%$; e.g., orthopaedic patients undergoing a 2-stage procedure, with history of implant/device *S. aureus* infection, and who are candidates for reimplantation
 - Free of any clinical and laboratory signs of active *S. aureus* disease on enrolment



WP 6D: Programme Management, Training, and Coordination

- To manage WP6 activities and ensure operational deliverables
- To ensure adequate training and qualification of the WP6 investigators in epidemiologic and clinical trial methods focused on prophylaxis, and provide additional programme-specific training
- To ensure operational coordination and strategic alignment across WP6A, WP6B, and WP6C, as well as within Topic 1 and ND4BB overall



WP6: Stepwise/staggered approach

- Call 8, ND4BB, Subtopic 1C to include indicative budgets on entire WP6: WPs 6A-D
- Eols being sought covering all WPs (WP6 A, B, C & D)
- WP6A and WP6D to start 2H2013
- WP6B and 6C will start 2H2014, with corresponding funding allocated stepwise based on agreed milestones review
 - Designs of WP 6B and 6C subject to change on the basis of the results of the epidemiological study (WP 6A), phase 1 safety/PK study conducted in USA, and regulatory input
 - Full consortium (including the sponsoring EFPIA partner) to determine the need for an Open Call to engage additional clinical sites/beneficiaries to conduct the 2 clinical studies based on the updated study details



Expected contributions of the applicants: Subtopic 1C



- Experts in active-surveillance, observational epidemiology, and clinical studies in ICU and surgical bacterial infections to participate in pan-European consortium
 - Expertise in immunointervention or prophylaxis for infectious diseases in the surgical and ICU populations
 - Project leadership and coordination infrastructure
 - Data storage, processing, and analysis capabilities
 - Hospital and healthcare institutions to join a clinical trial network with capability to run Phase 1, 2 & 3 clinical trials and epidemiology surveillance studies
 - Experts in diagnostics suitable for use in clinical trials, and in novel biomarker research
 - Clinical research organisation with global experience
 - Coordination & conduct of microbiology surveillance programs
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Expected (in-kind) contributions of EFPIA members: Subtopic 1C



- Clinical trial expertise
- Expertise in designing infectious disease epidemiology surveillance programmes
- Knowledge & expertise in antimicrobials R&D
 - Provision of study drug, regulatory support, project management, pharmacovigilance, clinical expertise, etc.
 - Training/oversight of clinical sites and labs to ensure they are “audit ready.”
- Non- Europe component of the clinical trial
- Project/alliance management personnel
- Workshops/seminars/Q&As.
- Statistics, PK/PD modeling & simulation expertise
- Clinical micro procedures/protocols/serology assays required in clinical trials
- Supplement study costs (up to 25%) incurred by public partners
- Gene sequencing/gene expression of *S. aureus* virulence factors



Questions?



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