

Introduction to IMI2 Antimicrobial Resistance (AMR) Accelerator programme (topic 2)

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Background and problem statement

The discovery and development of new prevention and treatments to address antimicrobial resistance (AMR) is an undisputed European and global challenge that is compounded by a low return on investment (RoI) for the pharmaceutical sector. This low RoI is driven largely by the lack of established reimbursement models and standard methods to express the true societal value for new technologies addressing AMR. This has subsequently led to a reduction in resources across the pharmaceutical industry and a decline in scientific discoveries. Overall this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link: https://ec.europa.eu/health/amr/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf). Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on a par with HIV and Ebola. Additionally, drug resistant tuberculosis (TB), which is the largest single contributor to AMR health, mortality, and economic impact.

There are significant scientific challenges to the discovery and development of new agents to treat and prevent AMR infections, including those caused by Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, and non-tubercular mycobacteria (NTM). As an example, despite there being an extensive number of essential bacterial targets, no novel mechanism antibiotics for Gram-negative infections have been approved in 40 years.

Furthermore, despite some recent progress, we have a poor understanding of how to rationally design potent small molecules that are optimised to treat life-threatening multi-drug resistant (MDR) Gram-negative pathogens. Models, approaches, and tools developed by large pharma or public entities to support antibiotic drug development need to be validated and shared more widely to serve the AMR community at large. At the same time, alternative approaches to treating infections require robust validation. The same is true for platforms that enhance the success of vaccines and monoclonal antibodies, or new imaging platforms to measure pharmacodynamic responses at the site of action.

In TB, the world's leading infectious disease killer with 1.7 million deaths in 2016, (from WHO TB report 2017, Executive Summary at the following link, http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf) there is an acute need for the

development of a novel combination regimen with an indication for the treatment of any form of TB ('pan-TB regimen') that will be more effective, shorter, and safer than current existing options. This applies to all types of TB (drug-sensitive (DS), multi-drug resistant (MDR) and extensively-drug resistant (XDR-TB)). A pan-TB regimen would encompass at least three new chemical entities, with properties better suited to protect against emerging resistance both individually as well as in combination. Many scientific hurdles must be overcome to understand how multiple chemical entities can be combined most successfully, keeping synergistic drug activity, drug-drug interactions, and translational aspects in mind. Regimen development in TB has provided and will continue to lead to learnings that will help to develop new treatments, including combination regimens, for other infections that have relied on mono-therapy thus far.

Overall objectives of the AMR Accelerator

The aim of the AMR Accelerator is to progress a pipeline of potential medicines, including but not limited to new antibiotics, to treat patients with resistant bacterial infections in Europe and across the globe or to prevent them. Specifically, if successful, projects in the AMR Accelerator are expected to deliver up to >10 new preclinical candidates and >5 'phase 2-ready' assets over a roughly seven-year period.

The AMR Accelerator provides, under one operational structure, a wide-ranging series of projects that addresses many of the scientific challenges in AMR. The scientific scope is broad, including prevention (vaccines, monoclonal antibodies (mAbs), immunoprophylaxis, other means) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive and Gram-negative bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within this broad scope, projects in the AMR Accelerator develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, progress potential new treatments through phase 1-3 clinical trials, and analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The AMR Accelerator will also potentially generate new clinical/regulatory phase 2-3 pathways. Over the past years, IMI's New Drugs for Bad Bugs (ND4BB) programme has created a vibrant drug discovery and development network in AMR, and met important milestones. The AMR Accelerator complements and augments the capabilities of the IMI ND4BB programme¹.

Progression of successful assets beyond the scope of the AMR Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms such as EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, Structural Funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance – January 2016 or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016 (<https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf>²) should be taken into account.

The AMR Accelerator programme will contribute to one of the three pillars of the European One Health Action Plan against Antimicrobial Resistance 'Boosting research and development and innovation in AMR' (June 2017: https://ec.europa.eu/health/amr/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf). The AMR Accelerator programme will also directly address the IMI2 JU objective to 'develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance' (Article 2(b)(iii) of the Council Regulation establishing IMI2 JU: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0557>)

¹ <https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb>

² For example, points 3 and 4 from the 'Roadmap for Progress'.

The AMR Accelerator programme structure

The AMR Accelerator programme consists of three pillars under which multiple actions are expected:

- **Pillar A:** Capability Building Network (CBN)
- **Pillar B:** Tuberculosis Drug Development Network (TBDDN)
- **Pillar C:** Company-specific Portfolio Building Networks (PBNs)

The two-stage IMI2 JU Call 23 includes one topic (topic 2) under Pillar A to complement the actions funded under IMI2 JU Call 15, IMI2 JU Call 16 and IMI2 JU Call 20.

For the new topic for Pillar A, launched as part of IMI2 JU Call 23:

- the indicative EFPIA in-kind contribution will be EUR 2 760 000

The EFPIA in-kind contribution will be matched by IMI2 JU funding across the whole of the AMR Accelerator and not necessarily 1:1 on an individual project or pillar basis.

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C will be a maximum of EUR 251 230 000.

Pillar A: Capability Building Network (CBN) to accelerate and validate scientific discoveries.

The CBN : 1) creates a coordination and support group to assist in the effective management of projects across the AMR Accelerator and; 2) delivers pre-competitive science to accelerate scientific discoveries in AMR, the results of which will be disseminated widely. The CBN includes projects to further basic science and discoveries to enable future drug discovery and development in the prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment of MDR bacterial infections including tuberculosis (TB), and non-tubercular mycobacteria (NTM). Although most research in the AMR Accelerator related to TB is conducted in the TBDDN (below), TB projects could occur in the CBN if the scientific concepts are of broader applicability (e.g. immunoprophylaxis).

The initial action in the CBN, COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7³, and containing the coordination and support group⁴, implements a coordination and support group that supports the operations of all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN action also focuses on the collection, sharing, and analysis of vaccine and/or antibacterial clinical trial data and the optimisation of animal infection models for bacterial infections.

The action in the CBN resulting from IMI2 JU Call 23 topic 2, will implement a research and innovation action to develop a framework for setting up antimicrobial resistance (AMR)-focused economic evaluations of vaccines and monoclonal antibodies (mAbs). A mathematical model will be developed and made publicly available to assess the impact of vaccines or mAbs strategies in the reduction of AMR.

Pillar B: Tuberculosis Drug Development Network (TBDDN) to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global TB epidemic.

³ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call15_CallText.pdf

⁴ For additional details see the topic 7 "Capability Building Network" of [IMI2 JU Call 15](#)

The TBDDN works to address the innovation gap in the discovery and development of a pan-TB regimen by combining access to novel drug candidates with innovative tools and incorporation of clinical trial data to accelerate the discovery of new combination regimens for the treatment of TB.

The platform is self-sustained and independent from other similar activities (Integrated Research Platform (IRP), TB Drug Accelerator (TBDA)). It is anticipated that there will be linkages with the TBDA (for more info on TBDA please visit: <http://partnerships.ifpma.org/partnership/tb-drug-accelerator-program>). It provides ready-to-use services for rapid progression of available (first line) new and innovative candidates. The platform is partly supported by the coordination and support group from Pillar A but includes management resources to self-sustain its scientific and financial reporting as well as innovation management procedures.

ERA4TB – 853989, selected under Pillar B from topic 8 of IMI2 JU Call 15 results in an action that creates a group to profile and progress anti-TB compounds from advanced lead through phase 1 and to collect, share, and analyse TB clinical trial data. Additionally, it addresses the development of new alternative anti-tubercular drugs (for example, host-defence or virulence approaches).

Topic 3 of IMI2 JU Call 20 will result in an action that will develop and implement innovative, state-of-the-art adaptive clinical trial designs for the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. Additionally, it will exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR.

As in the CBN, the overall scientific scope in the PBN is broad, including prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment (new antibiotics, non-antibiotic alternatives, formulation strategies, and combinations). Within this broad scope, the PBN provides a mechanism for dedicated partnerships between EFPIA companies and SMEs and/or academic teams for the discovery and development of new antibacterial assets, including in select cases TB and NTM. Assets and projects originate from SMEs, academia, or EFPIA companies, and are jointly progressed or studied, including both pre-clinical work and potentially phase 1-3 clinical development. The PBN is also potentially useful to generate new clinical/regulatory phase 3 pathways for pathogens such as NTM and to conduct phase 2 trials in TB.

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group⁵) is complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics, IMI2 JU Call 20 topic 3 and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, all grant agreements of actions under pillar B will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement⁶ will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the COMBINE – 853967 consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for COMBINE – 853967 to provide day-to-day support of projects in the AMR Accelerator programme, and will ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

⁵ For additional details see the topic 7 “Capability Building Network” of [IMI2 JU Call 15](#).

⁶ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

Furthermore, a memorandum of understanding (MoU) will be pursued between the Pillar B TBDDN actions (ERA4TB – 853989 and Call 20 topic 3) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 (EU-PEARL – 853966) to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable in each action resulting from ERA4TB-853989 and topic 3 of IMI2 JU Call 20. Similarly, when reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the AMR Accelerator (resulting from IMI2 JU Call 16) and TBDDN actions, as well as the IRP action of IMI2 JU Call 15 topic 1 (EU-PEARL – 853966), with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

Need and opportunity for public-private collaborative research

The discovery and development of new antibiotics and alternative treatment and prevention options for multi-drug resistant infections is a high medical and societal need. The AMR Accelerator will address multiple challenges in a coordinated programme, which offers excellent opportunities for collaborative work between different sectors and disciplines. Moreover, operating with the support of the coordination and support group in the CBN will allow for greater efficiency, by reducing the need for duplicative management structures or processes.

Due to the current low return on investment that developers can expect for agents to address AMR, this scientific area has not received the investment that was seen in the 'call to action' to address HIV/AIDS and on par with the public health threat. Consequently, public-private partnerships (PPPs) such as the framework provided by the IMI2 JU continue to be critical to that effort.

Excellent examples have been the previous and current investments by the European Union and IMI (ND4BB, Model-based preclinical development of anti-tuberculosis drug combinations (PreDiCT-TB), More Medicines for Tuberculosis (MM4TB), Open Collaborative Model for Tuberculosis Lead Optimisation (ORCHID), anTBiotic), the NIH (Tuberculosis Research Units Network, TBRU-N) and the Bill & Melinda Gates Foundation (TB Drug Development Accelerator and TB Alliance discovery portfolio). Multiple new drug candidates are in the pipeline for the treatment of TB for the first time in decades, and are reaching or about to reach the clinic. Existing drugs are being repurposed or optimised for TB with the potential of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for MDR-TB. In ND4BB, immense progress has been made from basic science to discovery of novel lead molecules through to running interventional clinical trials.

However, more work is critical to continue to address the constantly emerging global challenge of AMR. For example, there is a challenge of maturing the TB pipeline from the selection of candidates to progression through phase 1 studies, in addition to parallel studies to determine the optimal combinations to create new pan-TB regimens. Also, the ever-evolving resistance landscape requires additional investment to validate new tools and approaches, in addition to progressing potential new therapies to prevent and treat bacterial infections.

Acting to address these challenges in a single, coordinated Accelerator offers excellent opportunities for collaborative work between different sectors and disciplines in an area of critical scientific need.

The development of the AMR Accelerator will contribute to a vibrant AMR community in Europe and will offer potential opportunities for individual partners, such as:

- **Capability Building Network:**
 - Play key role in a EU AMR programme with connectivity to the broader global agenda on AMR;
 - Enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
 - Provide an opportunity to work within a broad network of researchers focused on AMR science and gain additional experience in AMR science and drug discovery.
- **Tuberculosis Drug Development Network:**

- Enable SME and/or academic groups to progress pre-competitive basic science project in the TB field;
 - Enable SME and/or academic groups to progress potential drugs from pre-candidate status through to 'ready for phase 2' status, including, but not limited to GLP and GMP scale up, formulation, toxicology studies, and phase 1 clinical studies, including preclinical combinations of drugs;
 - Provide the opportunity to work within a broad network on researchers focused on TB drug discovery.
- Portfolio Building Network:
 - Provide the opportunity for SMEs and/or academic groups to partner with EFPIA companies to enable progression of promising assets or technologies to key milestones, creating value and sharing risk. There will be potential to further extend such partnerships with EFPIA companies beyond the scope of the AMR Accelerator following project completion;
 - Allow a vibrant partnering ecosystem that will benefit SMEs or academics with early stage assets based on pre-agreed conditions and milestone decision points.

Applicants to Calls launched as part of the AMR Accelerator programme should consult the [IMI2 JU Model Grant Agreement](#) and [IMI2 JU Annotated Model Grant Agreement](#), as well as a short questions and answers document available at [https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions and answers on the AMR accelerator programme.pdf](https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions%20and%20answers%20on%20the%20AMR%20accelerator%20programme.pdf).

Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance

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Topic details

Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Vaccines

Specific challenges to be addressed by public-private collaborative research

Unmet medical needs

Antibiotics have greatly improved the health and life expectancy of human beings, but antimicrobial resistance (AMR) is rising, and deaths due to infections have been predicted to exceed the ones caused by cancer by 2050⁷. The World

⁷ <https://amr-review.org/Publications.html>

Health Organization (WHO)⁸ and the Centers for Disease Control and Prevention (CDC) of the United States⁹ have recently listed the priority human pathogens with threatening drug-resistance patterns. New generation antibiotics, vaccines and antibody-based biologics can all contribute to the response to the global challenge of antimicrobial resistant pathogens.

Challenges

Vaccines and monoclonal Antibodies (mAb) may reduce antimicrobial resistance (AMR). However, individual vaccine developers and manufacturers, as well as organisations developing mAbs and health authorities, acting alone, do not have the resources and the full expertise required to make a realistic and comparable assessment of the use of the different products on the reduction of AMR. This could instead be possible through the development of a mathematical model. For such a model to be representative of the concerns and interests of the various actors (i.e. industry and the public health sector), it should take into account the perspectives of these different actors in order to capture all relevant impacts both in terms of costs and health outcomes.

Therefore, quantifying the impact of vaccines and mAbs requires a broad collaboration involving partners from academia and industry to tackle the following specific challenges:

- **Measurement of the burden of disease (BOD) and costs of AMR:** there is a need for a disaggregation of the BOD by subpopulation to compare the cost-effectiveness of targeting strategies to go beyond the work performed by Cassini et al¹⁰ **Error! Reference source not found.** This would require a much more granular estimation of the burden to capture which subpopulation (e.g. migrants, elders, patients with certain comorbidities, surgery procedures, long-term care residents, etc.) are contributing most to the health burden, through which types of infection and which type of AMR. This granularity is critical to inform strategies that are most likely to reduce the AMR burden. The future burden estimations will also try to include potential incremental side effects such as increased disability, due to the fact that certain key surgery procedures will be less accessible thanks to the increased risk AMR will pose to the safety of surgeries. Once a more granular burden of disease is built, it could be possible to test which vaccine and monoclonal antibodies need to be prioritised and through which targeting strategy. As such, it requires access to multiple data sources to quantify the burden of disease and cost of AMR.
- **Limitation of models in capturing the complexity of AMR:** no model structure has yet fully captured (a) the direct effect of vaccines and mAbs in preventing bacterial infections and how this reduces morbidity and mortality, the spread of the pathogens (including antibiotic resistant strains) and the limit in the use of antibiotics to treat them; (b) the indirect effect of creating herd immunity (including the reduction of infection in immunocompromised, elderly and cancer patients); and (c) the variation in strain prevalence across countries and subpopulations. Modellers from academia should team up with modellers from industry to develop, test and make publicly available a more complex and complete model, taking into consideration academic, public health and industry perspectives.
- **Real data are not easily available to set parameters for the models.** This gap is frequently filled by running mathematical models with differential equations, which are based on assumptions that are not validated against real data. There is a need to generate new data and to use existing data from studies to improve the predictions.
- **There is insufficient information on the cost-effectiveness of vaccination and mAb strategies against AMR pathogens.** With so many pathogens and resistance profiles, there is a need to determine which vaccines and mAbs should be prioritised first and what population groups should be targeted. Scarce resources and opportunity costs require a more qualified approach than just generic statements on the

⁸ <https://www.who.int/en/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>

⁹ https://www.cdc.gov/drugresistance/biggest-threats.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugresistance%2Fbiggest_threats.html

¹⁰ Cassini et al have estimated the BOD in the EU but they did not forecast the BOD in specific target groups and they did not adjust the models “for age-specific risks, co-infections, appropriateness of antibiotic therapy, or for type of care, assuming common transition probabilities for all subgroups”.

usefulness of vaccines or mAbs to tackle AMR. Academic partners and industry need to agree on how cost-effectiveness should be estimated or what type of target population should be covered.

- **Model forecasts need to be validated.** The CDC and the ECDC rely upon surveillance systems that are far from perfect in terms of AMR standardised case definition and representativeness from states and countries. There is a need to calibrate the models by filling information gaps and verifying assumptions, on the basis of real data coming from the health care systems in a few pilot countries sourced from national information systems.

Scientific opportunity

Tackling the above-mentioned challenges will clarify which are the most cost-effective vaccines and mAb strategies to reduce infections and antibiotic consumption, increasing our ability to create a sustainable solution to AMR. It requires gathering the best European scientists, data analysts and data scientists, and modellers from academia and industry, to work together to make use of existing and future data, to develop specific models and to test, run and improve these models on publicly available platforms. This will allow regulators, policymakers, industry and HTA bodies to benefit from science-based evidence on the real impact of specific vaccines or mAbs on AMR. The success of the project depends strongly on complementarity between the academic partners specialised in model development, AMR assessment, epidemiology and health economics, and the industry partners with expertise on technical and clinical development, as well as on model development. Models are simplified versions of a complex reality and can be influenced by the approach taken by modellers who bring their own backgrounds, perspectives and training. Allowing an exchange of views and information between the various actors (in particular industry, academics, regulators, HTA bodies, and policymakers) will allow the improvement of the structure of the model and better inform its parameters, reducing thus both structural and parametric uncertainties in the outcomes. In addition, limiting industry-driven biases in model development will create a better chance that the policy options supported by the model outcomes will be acceptable to the decision makers who are frequently in the public sector.

Reasons for a public-private partnership

AMR has gradually depleted the antibiotic armoury and disaster will strike when the last class of antibiotics becomes ineffective. A model will have the benefit of predicting the reduction of AMR associated with novel mAb and vaccination strategies against AMR pathogens. This information should allow public health institutes and/or companies to select the right direction among several priorities. The results of the model shall then be used to better inform policy decisions which are more likely to be accepted and implemented if both the private and public sector perspectives are taken into account. Joining forces increases the chance that all points of view of the major actors feed into the analysis and produce final results that are *are more likely to be agreed upon* because they have been built through a consensus process¹¹. Whatever interventions and target groups will be prioritised, subsequent health interventions need to be financed through private and public resources and therefore it is important that both perspectives are taken into account during the modelling exercise.

Combining different perspectives, scientific interests, domains and expertise will create synergies that are not possible if academia or industry operate in isolation. The only way to address the challenges ahead is therefore through a public-private partnership that brings academia and industry together in a common effort.

Scope

The goal of the project is to **develop a framework for setting up antimicrobial resistance (AMR)-focused economic evaluations of vaccines and mAbs. The challenges include a measurement of the present rate of growth of AMR, its main drivers, its health and economic consequences, and which vaccines and mAbs might have the best chance of reducing the rate of AMR growth and the related health and economic consequences.** The model will build upon the work done by previous models in depicting the infection dynamics of

¹¹ As an example, when building Disability Adjusted Life Years lost because of AMR, the industry might be more inclined to give more weight to the productive age groups while the public-health perspective might give equal weight to all age groups.

key pathogens in specific populations that lead to antibiotic consumption and AMR, and will simulate the impact of mAb and vaccination strategies on the chain of events.

In a systematic review on AMR mathematical models, Birkegård et al [2] found that few selected studies fulfilled the TRACE modelling practice guidelines¹². The recommendations of the authors for future mathematical models on AMR included: “a) model the biological processes mechanistically, b) incorporate uncertainty and variability in the system using stochastic modelling, c) include a sensitivity analysis and model external and internal validation”.

The project has the following objectives:

- **Evaluate the burden of disease of AMR** by estimating inpatients’ (acute care hospitals and long-term care facilities) and outpatients’ infection rates in at least 8 EU countries for which suitable data is collected and available, as well as in the US¹³, and the relative attributable risk for morbidity, mortality and costs.
- **Build a comprehensive AMR model** (i.e. model structure, parameters, assumptions) based on an analysis of the strengths and weaknesses of existing models, and a gap analysis.
- **Collecting, gathering, and analysing data** from existing databases to feed the model.
- **Develop and test a cost-effectiveness analysis (CEA)** to estimate the cost and benefits of covering defined target groups (e.g. 18+, 60+, surgeries) with mAbs and vaccines.
- **Set up a study** to test, monitor, evaluate and improve the model.
- Ensure a **public and broad access to the model**.

The model and studies should not target specific bacteria, but should apply as a general tool adaptable to various bacteria.

Collaboration agreement(s)

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group¹⁴) is complementary to all the grant agreements of other actions selected under Pillars A, B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics¹⁵, IMI2 JU Call 20 topic 3¹⁶, IMI2 JU Call 23 topic 2 and related grant agreements).

The respective options of Article 2 (complementary grant option), Article 31.6 (complementary grant option) and Article 41.4 of the [IMI2 JU Model Grant Agreement](#) will be applied. Accordingly, the consortia selected under this topic from the AMR Accelerator Pillar A will conclude a collaboration agreement with the COMBINE – 853967 consortium selected from IMI2 JU Call 15 topic 7. This collaboration agreement will provide the framework for COMBINE – 853967 to provide day-to-day support of projects in the Accelerator, and will ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

¹² TRACE is a general framework for documenting a model’s rationale, design, and testing. The TRACE guidelines include the following 8 elements: “1) Problem formulation (clear formulation of the objective and a description of the context of the model); 2) Model description (written description of model elements to allow readers to understand and replicate the model); 3) Data evaluation (an assessment of the quality of data used to parameterise the model); 4) Conceptual model evaluation (a list and explanation of the most important conceptual design decisions); 5) Implementation verification (internal validation of the model, testing for programming errors and assessing model performance); 6) Model output verification (external validation, testing whether the model output matches the observations); 7) Model analysis (mainly sensitivity analysis); 8) Model output corroboration (a comparison of model output with data that were not used to create the model)

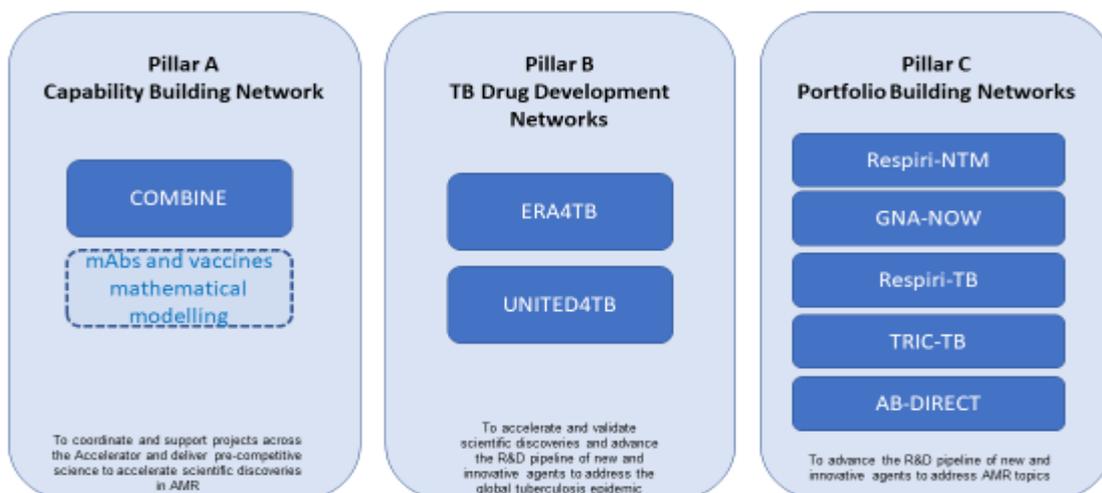
¹³ Access to data from the US will be provided by the EFPIA Partners who have licenses to databases.

¹⁴ For additional details see the topic 7 “Capability Building Network” of [IMI2 JU Call 15](#).

¹⁵ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call16_CallText.pdf

¹⁶ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call20_CallText.pdf

The AMR Accelerator



The action in the CBN resulting from this topic 2 in IMI2 JU Call 23, will implement a research and innovation action to develop a framework for setting up antimicrobial resistance (AMR)-focused economic evaluations of vaccines and monoclonal antibodies (mAbs). A mathematical model will be developed and made publicly available to assess the impact of vaccine or mAb strategies in the reduction of AMR.

Expected key deliverables

- Burden of Disease caused (BOD) by AMR. The systematic review of the literature on the BOD of AMR will lead to an **epidemiological repository** of incidence, prevalence, disability (e.g. disability-adjusted life years – DALYs, quality-adjusted life year – QALYs), mortality, short- and long-term disability, consumption of antimicrobials, costs and other parameters associated with main pathogens and population groups. The repository will provide the basis for the estimation of the BOD caused by infectious disease and the contribution due to AMR. This repository will be complementary to the following existing databases:
 - In comparison with to the current ECDC database and any relevant valuable national database on AMR that is based on laboratory reporting, this repository will provide all the estimates available in the literature, with more information, for example, on incremental costs associated with AMR from case control studies.
 - Similarly, the notifications of infectious diseases of the ECDC database are very useful for surveillance, but cannot be used to estimate or infer population incidence. The project repository will provide a rich data source of the incidence of pathogens by target group derived from the literature.

Reliability should be ensured by a thorough quality control policy to be implemented before placing any information on incidence of infections in the repository, with a description of the method used to estimate the incidence.

For this deliverable, the consortium should particularly, where appropriate, build on existing work, avoiding duplication of efforts.

- A **systematic review of mathematical models** on the effect of vaccines and mAbs on AMR. The review should include the analysis done on the impact of vaccines against main bacteria such as, for instance, pneumococcus or *Haemophilus influenzae*. This will help to identify the strengths and weaknesses of existing models, and suggest new data gathering and analytical strategies to tackle limitations and fill gaps.

- Construction of a **mathematical model**. The mathematical model should be developed on an open-source basis and be made available to the research and scientific community at the end of the project. The structure will build upon what has already been done and will consider potential entry points in which real data could anchor the model to real operational settings as examples of AMR control. Examples include the screening at admission for methicillin and carbapenem resistance in a sample of hospitals, not only in the EU but also possibly in the US where additional data are available. In mathematical modelling, the main problem is to parametrise the model. It is unlikely that all the parameters could be available just using data from EU countries and for this reason, some extrapolations would be needed from the literature. Some parameters for which there is insufficient information from published studies carried out in the EU may require some inference to be deduced from the US studies, as most of the published research currently comes from there. For example, it is frequently difficult to have the attributable costs or the attributable mortality due to AMR per se (taking into account comorbidities).
- **Economic evaluation of alternative mAbs and vaccines** strategies. Several scenarios will be tested, comparing mAb vs vaccines, and different mAb strategies separate from different vaccine strategies. The comparator will be existing AMR control strategies. Different approaches leading to different scenarios would have to be presented and tested in sensitivity analyses in order to assess their impact on model outcomes. The potential biases and validity of each scenario should be discussed, without excluding the possibility of using an alternative scenario as the base case.
- The results will suggest the strategic directions on where to invest and the relative target product profiles of mAb and vaccines.
- Monitoring and evaluation plan. A detailed multi-year plan on how to monitor AMR will be tested in a few countries to verify the assumptions and predictions of the model.

Expected impact

The **epidemiological repository** that will be obtained in Work package 1, besides providing a transparent basis for the BOD estimation, will be made accessible through an internet database to be designed within the project. Any researcher will benefit from using the most comprehensive database on the epidemiology of infectious diseases and resource consumption associated with sensitive and resistant pathogens. Producing a reliable repository with clear description of the methods used to derive the estimates of the BOD and AMR will benefit the credibility of the results of the mathematical model. During the project, the access will be free of charge. After the end of the project, the conditions for access will depend on the operational model to ensure the maintenance and sustainability of the databases, and compliant with the IMI2 JU intellectual property policy. The ambition is to favour open access as much as possible.

The results of the mathematical model (publicly available and free of charge) will allow policymakers and healthcare managers to make informed decisions on vaccines and mAb strategies. The impact will include clear direction for EFPIA partners and health care authorities on which research and development strategies should be prioritised to reduce AMR through vaccine and monoclonal antibodies.

Better chance of preserving the efficacy of last-resort antimicrobials. As an example, the European Centre for Disease Prevention and Control has published guidelines for the screening of patients at high risk for Carbapenem Resistant Enterobacteriaceae (CRE) and Carbapenemase Producing Enterobacteriaceae (CPE) at the time of admission [3]. The retrospective record review will provide an assessment on their status of implementation and will allow estimation of the resources required to put in place a functional screening and surveillance system for CRE and CPE, as well as other types of resistance.

Testing the sustainability of the study approach by financing a multi-year monitoring and evaluation system in key health units of a few pilot countries. The impact will be a strengthening of the existing AMR surveillance systems, and a verification of the assumptions and parameters underlying the model. For example, an initial model focused on a specific vaccine or mAb might provide an initial base which will be fine-tuned according to real data, and which will be further expanded to other promising mAbs and vaccinations, with further fine-tuning.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards¹⁷;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures¹⁸;
- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation¹⁹/dissemination²⁰ obligations must be considered to maximise impact:

- Ensure that the models that will be developed remain available online and updated after the end of the project and for a period up to 5 years.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures²¹ in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- GlaxoSmithKline Biologicals
- Janssen Vaccines & Prevention
- Pfizer

The industry consortium plans to contribute the following expertise and assets:

- GlaxoSmithKline Biologicals

Expertise: epidemiology, biostatistics, infectious disease modelling, health economics, database management, web design, vaccine pre-clinical and clinical science, mAb pre-clinical and clinical science, translational research, immunology, phenotypic and genetic characterisation of microbial strains.

Model development: allocation of a dedicated modeller to co-develop the model with other partners.

Databases access: access to CPRD (Clinical Practice Data Linkage) and IBM Truven Marketscan (including US data).

- Janssen Vaccines & Prevention

Expertise: clinical development, market access and modelling.

¹⁷ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

¹⁸ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

¹⁹ Article 28.1 (Additional exploitation obligations) of the [IMI2 Grant Agreement](#) will apply.

²⁰ Article 29.1 (Additional dissemination obligations) of the [IMI2 Grant Agreement](#) will apply.

²¹ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Model development: allocation of a dedicated modeller to co-develop the model with other partners.

- Pfizer

Expertise: clinical development, market access and modelling.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 6 500 000.

The indicative in-kind and financial contribution from EFPIA partners is EUR 2 760 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, considering the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture, which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

- Epidemiology;
- Statistics;
- Health Economics;
- Microbiology;
- Laboratory techniques associated with AMR;
- Database management, data scientists;
- Database web programming;
- Computational and mathematical modelling in infectious diseases;
- Management Information Systems;
- GDPR compliance.

The consortium should involve and associate key actors from academia that have conducted/are planning to conduct mAb clinical trials or are involved in mAb research.

- It is important to involve public health agencies/authorities because their expertise can substantially contribute to the scientific soundness of the study and because it is important to add their perspective²². This will ensure that the project will fully consider public health needs and is not mainly driven by pharma industry. Regulatory authorities could also have an interest to be involved in the consortia to ensure the design of the model will meet their expectations.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

It may also require mobilising, as appropriate, the following resources:

- Access to CDC and ECDC databases;
- Expertise in dealing with data (retrieve, curate and analyse data), including data coming from US databases;
- Access to hospital information systems and general practitioner databases for the retrospective data collection;
- Access to the health information systems in the countries selected by the applicants.

Considerations for the outline of project work plan

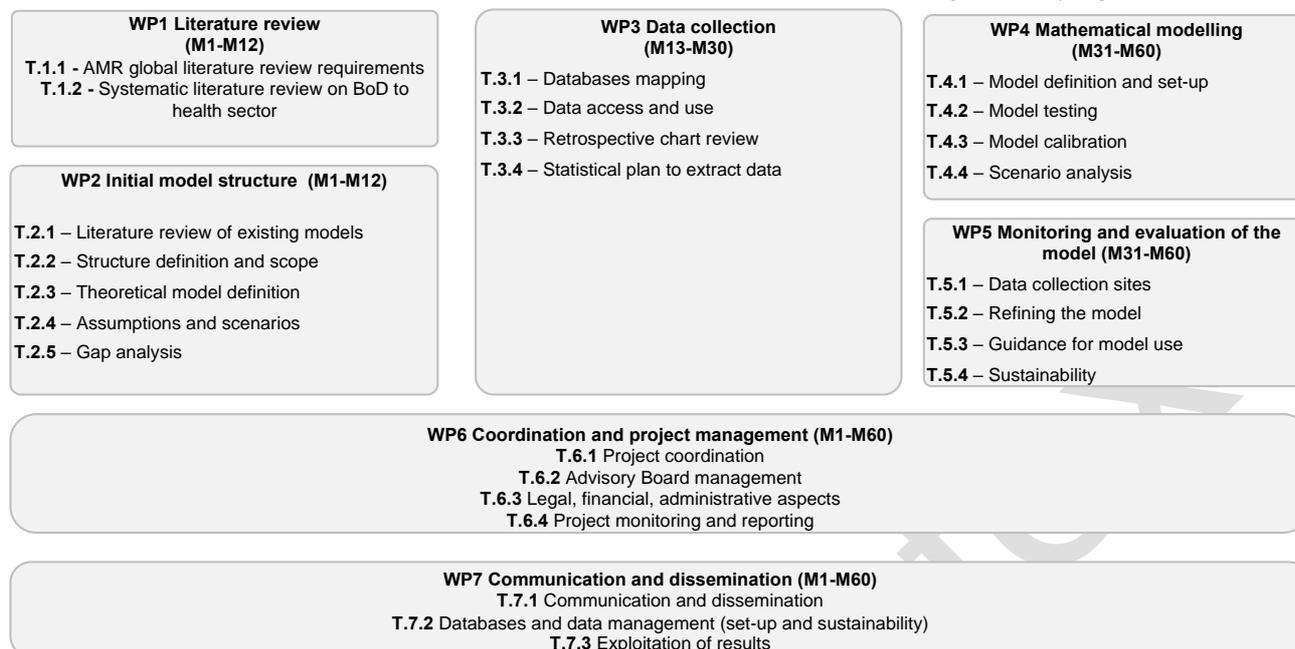
In their stage 1 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of enough resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ health technology assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

²² To avoid potential conflicts of interest or issues from PHA to participate in a consortium with EFPIA partners, the applicants should propose the best and most realistic way to include these organisations.

Legend: WP: workpackage T: Task



Work Package 1 – Burden of disease due to AMR

The goals of this work package are:

The estimations of the inpatients' and outpatients' infection rates should at least be sorted by sensitive and resistant pathogens by population group (e.g. age, presence/absence of comorbidities), by type of disease, by type of surgery and other specific categorisation of patients.

Work Package 2 – Model structure development

These developments could include different activities such as:

- Conducting a systematic review of the models used to predict the influence of mAbs and vaccines for treatment or prevention. The review will help to clarify model structure, parameters, assumptions, strength and limitations, and gaps to be filled.
- Clarifying the scope: AMR is a universal and a complex phenomenon. Bacteria develop resistance by natural selection even without the use of antibiotics and this fraction of natural AMR is rarely taken into account. Such natural selection is speeded up when antibiotics are used for animal and human health and then antibiotics are released in the environment, ending up in the food chain. Covering all the variables influencing the complexity of AMR development in the different sectors (natural development, food production, veterinary health and health care) would be impossible, and a narrower focus is needed to make the study manageable. The model is likely to cover the health sector, leaving out the contribution of the veterinary and agricultural sectors and the natural selection of resistant strains.
- Identifying assumptions and information gaps in parameters will involve a review of the disease ecological dynamics, notably:
 - Natural history of disease for sensitive and resistant pathogens in the general population or in health care settings including asymptomatic incubation, latency, infective stage, differential probability of transmission between a susceptible and a resistant strain, fitness costs, probability of acquiring resistance if exposed;
 - AMR Diagnostics sensitivity, specificity and positive/negative predictive values;

- Attributable outcomes by sensitive and resistance pathogen considering comorbidity, age and other confounders;
- Type of antibiotic consumption, with a special focus on carbapenems, extended spectrum beta-lactamase, fluoroquinolones and 3rd generation cephalosporines and the probability of acquiring specific resistance if exposed to these antibiotics.

Work Package 3 – Data gathering

The goals of this work package are:

Databases already identified by industry include the Marketskan²³ and other claims (e.g. Kaiser Permanente) databases in the US, the NHS²⁴ and GP databases²⁵ in the UK, the Epidemiologie – France Portal Health Database²⁶, the health care database of the German Institute of Medical Documentation and Information²⁷, Health for All Italia²⁸. Examples of data to be collected from databases include MRSA and CRE screening and isolation carried out in US and UK hospitals, as well as similar national surveillance data from the EU Member States. This care-focused approach has the main objective of operationalising the issue of AMR by modelling different impact pathways for vaccines and mAbs while narrowing the scope of both to nosocomial transmission. This approach will also geographically focus on the EU as priority settings because data are available and screening processes are in place for priority pathogens. Besides providing a specific operational context, this focus on MRSA and CRE screening also has the advantage of being of high priority in EU countries' policy agendas.

Work Package 4 – Cost-effectiveness analysis (CEA)

The cost-effectiveness will be estimated for alternative target product profiles. The WP4 will for instance have to decide:

- Which vaccines and mAbs should be included in the model. The first skeleton of the model will be based on previous assessments of the impact of existing vaccines, for example the impact of Pneumococcal Conjugate Vaccine on penicillin non-susceptible strains and the impact of influenza immunisation programmes on antibiotic prescription. This initial assessment will provide a better idea of how experience has tried to depict the patient pathways through which prevention of infection on specific bacteria and viruses can impact antibiotic consumption, AMR, health outcomes, resource consumption and costs. This initial model construction could be expanded to other vaccines and mAbs, generating several potential models and identifying common elements which could produce a core structure which could be adapted to model the impact of other vaccines and mAbs.
- Whether or not to limit the perspective to health care costs or to add social costs, too. Examples of health care costs include lengthier hospitalisation of AMR hospital infections vs the same type of infection due to sensitive bacteria. Costs will take into account the different health care systems of the EU and other countries. Cost comparability will have to consider inflation adjustment for estimates taken in different time periods, and the exchange rates of different currencies vs the reference currency (e.g. USD). An example of social costs might include lost income due to incremental length of hospitalisation and other social consequences.
- What to include in the existing standard of care (comparator). The incremental benefits of mAbs and vaccines will be compared with existing preventive strategies (e.g. Methicillin Resistant *Staphylococcus aureus* (MRSA) screening and isolation), stewardship for the correct antibiotic prescription, and similar existing activities.

²³ <https://www.ibm.com/products/marketscan-research-databases>

²⁴ <https://www.nhs-database.co.uk/>

²⁵ <https://www.cprd.com/home/>

²⁶ <https://epidemiologie-france.aviesan.fr/en>

²⁷ <https://www.dimdi.de/dynamic/en/further-services/health-care-data/>

²⁸ <https://www.istat.it/it/archivio/14562>

- The patients' pathways by type of health care setting. This includes the various steps patients go through between admission and discharge (e.g. carbapenem resistant screening and isolation) to capture all the costs due to resource consumption and the transmission dynamics (e.g. in the case of not complying with screening and isolation).
- The strategic options will be evidence-based, through the selection of interventions on the basis of their demonstrated efficacy in clinical trials, their feasibility and operational effectiveness in clinical settings, and their targeting strategies to provide the most health gains and economic savings.
- Predict potential impact of novel vaccines and mAbs against AMR in reducing the emergence of resistance.

The model should also inform future research agendas by exploring the impact of uncertainty around (expected) data gaps. Notably, to explore uncertainty around 1) attributable incidence of resistance acquisition due to antibiotic exposure, and 2) differential probability of transmission between susceptible and resistant strains (fitness cost). This exploration will help to identify drivers of both structural and parameter uncertainty on costs, impact and cost effectiveness, therefore setting future research agenda items.

Work Package 5 – Evaluation

The goals of this work package are:

The objective is to set up a long-term monitoring and evaluation strategy to calibrate the model. This will be done by building a monitoring and evaluation system in a few pilot countries to verify certain assumptions of the model and the reliability of parameters. The type of data, the structure of the data gathering and reporting will depend on the knowledge acquired from WP1–WP4. Attempts will be made to find out whether or not the COMBACTE network (e.g. COMBACTE –MAGNET) or other consortia have carried out similar types of management information systems to evaluate the results of AMR models.

Work Package 6 – Coordination and Management

The goals of this work package are:

The project will require strong coordination between the partners and regular follow-up of progress. A steering committee will be formed by representatives of EFPIA and BRF (Beneficiaries Receiving Funding) to steer the direction towards achieving the objectives. The coordinator will set up a project management office to ensure strong coordination and management.

In addition, the model should be tested under a collaborative study that should be developed as a horizontal activity within WPs 2, 3 and 5, in which an academic partner will be the sponsor, responsible for recruiting other academic institutions and hospitals that will participate in the implementation of the study. The sponsor institution will appoint core staff in charge of managing the study.

Work Package 7 – Communication and Dissemination.

The goals of this work package are:

The progress of activities will be summarised on a website or in newsletters that will be distributed at regular intervals to all partners. Scientific publications will also be prioritised to inform about the model and draw attention of the vaccine and modeller communities. General annual meetings will be convened to summarise annual achievements in project WPs and a final Workshop will provide the overall results. Dissemination of results will be carried out also by participating in scientific conferences and annual meetings from public health agencies (e.g. PHE annual meetings).

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.²⁹

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project³⁰, and updated during the project lifetime and could include identification of:

- Different types of exploitable results
- Potential end-users of the results
- Results that may need sustainability and proposed sustainability roadmap solutions

Enough resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).³¹

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

²⁹ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

³⁰ As an additional dissemination obligation under Article 29.1 of the [IMI2 Grant Agreement](#) will apply.

³¹ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

References

- [1] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; 19 (1): 56–66. [https://doi.org/10.1016/S1473-3099\(18\)30605-4](https://doi.org/10.1016/S1473-3099(18)30605-4)
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