TECHNICAL ANNEX

COST Action proposal

"AMICI"

Anti-**Mi**crobial **C**oating **I**nnovations
to prevent infectious disease

COST is supported by
the EU Framework Programme
Horizon 2020

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1. S&T EXCELLENCE

1.1. Challenge

1.1.1. Description of the Challenge (Main Aim)

Infections and infectious diseases are a continuous threat to human health. According to the European Centre for Disease prevention and Control (ECDC), over 4 million people are estimated to acquire a HealthCare Associated Infection (HCAI). The number of deaths occurring as a direct consequence of these infections is estimated to be at least 37 000, and these infections are thought to contribute to an additional 110 000 deaths each year. In February 2015, the European Commission released a progress report on the 5 year action plan against the rising threats from AntiMicriobial Resistance (AMR) that was initiated in 2013. Key actions are focussed on an appropriate use of antimicrobials, effective prevention of microbial infections, development of effective antimicrobials (antibiotics) or alternatives, joining forces with international partners, and reinforcing research to combat AMR in an innovative way. However, the number of infections caused by multi-drug resistant bacteria continues to increase at a significant rate and resistance to last-line antibiotics continues to concern Europe. Vytenis Andriukaitis, European Commissioner for Health and Food Safety has recently said that AMR is one of the most pressing public health issues of our time.

The AMICI-consortium is convinced that new methods, in addition or as an alternative to an appropriate use of disinfectants and antibiotics, are required to reduce microbial activity, associated infections and the increase of AMR. There is an urgent need for the European Commission to expand their investments in these alternatives. A potential and promising weapon against bacterial growth and possibly the development of multi-drug resistant bacteria has been found in AntiMicrobial (nano)-Coatings (AMC). In coatings fortified with an active ingredient, the ingredient is responsible for the elimination of the microorganisms.

Nowadays, a wide range of AMC is commercially available and has been applied or investigated by network partners. A recent study showed that 50% of the coatings contain nanosilver, and that these perform best in the ISO test for efficacy. Nevertheless, silver release has been suggested to cause new forms of AMR, and the release into environment will cause problems in regulation. An existing COST Action iPROMEDAI particularly aims at research on timed presentation and local delivery of antimicrobial active compounds from medical devices, such as catheters, to reduce the incidence of device-associated infections that originate from bacteria developing in biofilms. The AMICI Action network will focus on innovative AMC on non-invasive materials and surfaces, such as operating tables, walls, the interior of ambulances, door handles, textiles etc.

So far, little is known about the effectiveness of the application of AMC on surfaces on the prevention of spreading infections and their impact on induction of multi-drug resistant bacteria in the healthcare (e.g. hospitals and nursery homes). The presence of active substances in AMC may promote / induce resistance mechanisms and this needs to be understood and alternative strategies sought. A balanced risk-benefit analysis of its widespread application is needed to guide a ‘Safe by Design’ development and introduction in complicated chains with high demand for compliance such as healthcare.

Reasons for the so-far limited introduction of innovative AMC in Healthcare include:

- Systematic, international coordinated research on the effects (both positive and negative) of AMC in heathcare or other sectors is not yet available.
- There is a lack of know-how regarding the availability and use of different materials and mechanisms of action of (nano)-coatings and the desired use in different applications, procedures and products.

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- Little to no information is available on the possible adverse effects of AMC, e.g. the potential induction of new resistance mechanisms in bacteria or emission of toxic agents into the environment.
- The lack of a standard performance assessment for AMC, applicable in laboratory settings makes it difficult to directly compare the different coatings from different producers.
- Laboratory tests only check the functionality of coatings in a(n) (extreme) test condition, field tests or benchmark methods to assess the efficacy in field conditions are lacking. There is no communication or publication of best-practices by individual hospitals or the suppliers.

Challenge to value chain

The above issues are the major challenges of this consortium and its members hypothesize that introduction of (nano-based) AMC into hospital settings can offer a number of new opportunities to prevent infections and the induction of multi-drug resistant bacteria. However, before these coatings can be widely used in healthcare, new challenges have to be met. Firstly, there is an urgent need to establish a representative field or field simulation test, to describe the actual performance of coatings, and directly relate the outcome of this test to an actual status of HCAI. The model below illustrates what the role of the coatings is suggested to be.

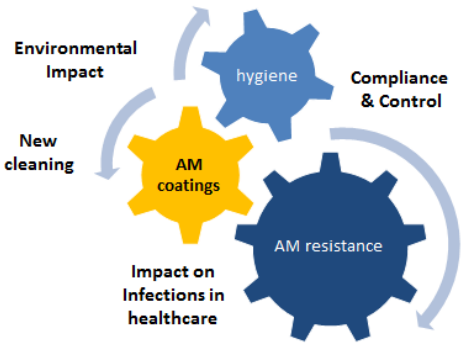

Figure 1. The enabling role of AMC in reduction of AMR as an alternative to antibiotics, and changing the cleaning procedures, thereby reducing efforts for hygiene control, reducing total costs and at the same time causing extensive reduction in environmental impact of disinfection control

Challenge for the entire chain

Although we claim that the introduction of coatings will decrease the environmental impact of conventional cleaning and its chemicals, the toxicological impact of AMC itself has to be examined, as well as the possible development of AMR to (the active ingredient of) coatings. Although the appearance of resistance is mainly linked to the use of antibiotics, bacteria have become resistant to some biocides such as Triclosan. The potential to develop such resistance has been debated for several years. Although most of the producers of active ingredients with antimicrobial action state that their ingredient does not lead to the development of resistant organisms, there is insufficient evidence to prove and generalise that statement. For these investigations there is no standardised method to predict if an active ingredient invokes either resistance or cross-resistance.

Challenge for suppliers

AMC with an active ingredient need to comply with the new European Biocidal Products Regulation. A new Regulation, the first to build in the new Commission definition on Nanomaterials, is meant to simplify and streamline the requirements for approving active substances and authorizing products. All currently used active ingredients need to be submitted to ECHA (European Chemicals Agency) before 01-09-2016. Therefore, a further assessment for different antimicrobial products is required with regard to identify and release of (active) ingredients from the coatings into the environment.

The COST AMICI Action aims to:

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- develop and maintain a European network including producers, distributors, processors of AMC, and (potential) users of AMC in healthcare, as well organisations involved in the compliance with (international) standards on hygiene. (WG1-5)
- consult and support policy and the healthcare sector with regard to further actions and application of AMC against microorganisms and the prevention of the spread of infectious diseases. (WG1-5)
- use the know-how and expertise of the network to stimulate development and optimisation of antimicrobial materials for non-invasive surfaces. (WG1)
- develop standardised methods to evaluate and compare the effectiveness of coatings in a laboratory setting, with possibilities to extrapolate the method to field tests. (WG2)
- develop field tests that enable the evaluation of the effectiveness of the use of AMC in the prevention of the spread of infections in various settings within the healthcare sector. (WG2)
- gather information on the impact of the introduction of AMC in various settings on the development of multi-drug resistance, and the possible development of AMR to AMC. (WG3)
- establish an approach for a risk-benefit analysis for using AMC in different healthcare environments, weighing potential adverse effects (e.g. eco- and cyto-toxicity) versus long-term savings and benefits. (WG3)
- determine the effects of (semi)-permanent coatings on procedures and downstream effects (costs, sustainability) in the cleaning process in healthcare (the new cleaning approach). (WG4)
- disseminate knowledge on AMC innovations to stakeholders such as coating suppliers and healthcare sector (WG5)
- disseminate the developed knowledge on laboratory and field tests to relevant stakeholders, including test labs, producers and users. (WG5)
- disseminate findings on the new cleaning procedures and logistics upon introduction of AMC into healthcare and other sectors such as food processing industries. (WG5)

1.1.2. Relevance and timeliness

A network on AMC innovations is highly relevant and timely. As the number of infections caused by multi-drug resistant bacteria continues to increase, so does the need for counteractive measures. Industrial research and development in the field of AMC are advancing and have already been quite successful. However, healthcare environments cannot fully embrace AMC until these coatings have been field tested with respect to their performance, and comprehensively researched for possibly toxic emissions and impact on AMR. Therefore, there is an urgent need for translation of available knowledge and innovations into healthcare practice such as hospitals and nursery homes. Billions of HCAI-related costs combined with an ageing, and therefore more vulnerable population, underlines the need for a network that brings together available knowledge and expertise and tackles the issues at hand. A thorough analysis of the risks and benefits of AMC application will prevent unnecessary stagnation – ensuing the new regulation – of their widespread application.The EC action plan against the rising threats from AMR (2011) pays little attention to alternatives like AMC.

1.2. Objectives

1.2.1. Research Coordination Objectives

The main objective is to develop, structure, coordinate and maintain a long-term, flexible and open European network in the field of AMC in healthcare. The scientific field encompasses R&D of materials and coatings, testing, legal aspects and cleaning methods. Research coordination will not only include knowledge institutes, such as universities and applied science institutes, but will also incorporate producers, distributors, processors, policy makers and (end) users of AMC to ensure the best possible effectiveness and cross-fertilization.

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Research coordination to be achieved within this Action, will employ an interdisciplinary approach in order to bridge the fields involved and thus achieve high-impact results. The Action aims to coordinate international research efforts which will also include the collection and identification of information and data on AMC and performance assessment – with separate WG's dedicated to performance assessment and risk-benefit analysis.

1.2.2. Capacity-building Objectives

AMICI aims to strengthen AMC-related capacity in various ways and at different levels. Knowledge on the effects of AMC in healthcare (and other sectors) is continuously newly generated or even already available, in both the academic world and with industrial partners. But it is still fairly fragmented. This Action will provide coordination of international and intersectoral research efforts, by a variety of activities such as collaborating with existing projects, organizing new events, jointly developing and implementing working groups, etc. so that forces can be joined in combatting AMR.

Closer collaboration and increasing organisation of available knowledge, will disclose state-of-the-art nanotechnology and biotechnology knowledge, not only in the academic world but also to industrial partners. This will empower the latter to create more effective AMC and translate their innovation into tangible and successful new market applications. Not only will have this a great societal impact in terms of healthcare improvement but it has considerable economic benefits as well, as it will strengthen competitiveness of the sector.

The Action strives to create a set of guidelines for stakeholders involved, containing standards, regulations, recommendations, etc. based on which they can select the appropriate safe and effective applications. This will support suppliers in developing safe-by-design coatings, a.o. based on available knowledge on possible adverse effects. It will also enable users in healthcare to make an informed decision on which type of application is best suited for their individual environment.

1.3. Progress beyond the state-of-the-art and Innovation Potential

1.3.1. Description of the state-of-the-art

Novel antibiotic drugs are scarce and increasing resistance against antimicrobial drugs is established. Innovations that tackle rising and prominent threats in healthcare are demanded. Preventive innovations are needed to minimize microbial pressure in bacterial “hotspots”, like hospitals, nursing homes or daycare centers. For example, bacteria can persist for many months on inanimate surfaces, forming an ongoing source of transmission. Healthcare workers can transfer these microbes to the patient after touching contaminated surfaces. Also, biofilms harboring pathogenic bacteria can form on the surface of medical implants after surgery and are a source of poorly treatable recurrent infections. A state-of-the-art innovation to combat pathogenic bacteria is the creation of self-disinfecting surfaces through the application of coatings with antibiofouling and/or bactericidal properties. Particularly bactericidal coatings are interesting in healthcare because of the capability of these coatings to kill pathogens on contact. Many different chemical strategies and technologies for antibacterial coatings have been described. Antibacterial coatings may contain active eluting agents (eg, ions or nanoparticles of silver, copper, zinc, or antibiotics, chloride, iodine, etc), immobilized molecules that become active upon contact (eg, quaternary ammonium polymers or peptides), or light-activated molecules (eg, TiO_2 or photosensitizers). As depicted in a recent market analysis (source: marketsandmarkets.com), the global market for these coatings is growing. With an estimated market worth of $1.5 billion, the global AMC demand is expected to reach $2.9 billion in 2018. Only few studies are available on introduction of these AMC in healthcare, nevertheless results are promising indicating long-term efficacy of self-disinfecting coatings on surfaces. Clinical trials show that copper as an antimicrobial agent continuously reduces the bacterial burden by 83% and reduces the risk of infection by 58%. The evaluation of functional efficacy relies

on conventional microbiological tests which are time consuming, highly labour intensive, difficult to standardize and field tests are lacking.

1.3.2. Progress beyond the state-of-the-art

So far, only little information has been published on the results of introduction of AMC in healthcare. In an intensive care unit in Los Angeles County, the application of AMC on various fomites such as bed rails, tray tables and walls was studied. The AMC assessed in the study was found to have persisted over 15 weeks in reducing the total amount of bacteria and antibiotic resistant bacteria on surfaces. The CuViTo FP7 program that ended in 2013 was working on manufacturing a copper-based AMC, but results on validation of the AMC in hospitals are not available (yet). Also, the SelfClean project mentions progress in the development of self-cleaning, antibacterial coatings based on the incorporation of doped TiO_2 nanoparticles in Sn-Ni matrix, but validation studies of these coatings are not yet available.

1.3.3. Innovation in tackling the challenge

Starting from AMCs that are currently being developed or that are ready for validation the network will combine all available results on AMC innovations to futher develop AMC ready to use in healthcare. Innovative research on AMC and possible adverse effects, such as toxic emissions and development of AMR will be undertaken. Development of field tests and benchmarking of AMC will take place. Validation studies of AMC in healthcare, including new cleaning concepts will be performed.

1.4. Added value of networking

1.4.1. In relation to the Challenge

Increasing human traffic and trade between different countries in Europe contributes to the spread of multi-drug resistant organisms and a pan-European approach is needed to tackle the problem. AMR is a global public health concern. Therefore, knowledge and best-practices of application of newly developed AMC have to be disseminated throughout Europe (and even globally) to help reduce the development and spread of multidrug resistant microorganisms.

This network gathers partners from top research centres, producers and processors of AMC in different environments, as well as organizations involved in the compliance with international standards on hygiene, with an emphasis on antibiotic resistance. Since bacterial resistance is not confined to only hospital environments, this network will take a lifecycle approach, taking into account all products and environments that are involved. A lot of knowledge is already available with respect to AMC, but it is fragmented due to its origin, its biological effect and application in different sectors. The set-up and cross-overs reached by this consortium will allow combination of available knowledge and stimulate further development and application of innovative and efficient antimicrobial products. The added value of combining different networks and sectors is that best-practices and accumulated knowledge can be exchanged. In addition, this network will actively enable the translation of know-how on the application of AMC from other sectors to healthcare, as so-called crossovers. This may lead to a reduction in the spread of infection episodes and to an increase in the efficacy in the fight against bacterial resistance to current antibiotics. Each partner in the AMICI network has a unique and valuable expertise empowering the strength of this multidisciplinary and complementary consortium.

The introduction of a new European regulation on the usage of biocides raises the concern that active ingredients currently used in AMC will be disallowed after 2016. Producers of coatings with active ingredients need support from the European network to assess the different antimicrobial products used in coatings. Their participation in this network will give an added value to the potential of their products as well as the estimation of its impact in healthcare, based on experience and tests

elsewhere. This will help to improve products and their applications to fight resistance in a responsible manner. Different test standards are used to assess the effectiveness of AMC. The coordination of this European network will lead to the development; standardisation and dissemination of a validated rapid-screening test for AMC that takes into account both antimicrobial activity and the possible development of microbial resistance. This is essential to evaluate and compare different AMC used in Europe. It makes benchmarking possible, stimulating producers to go for the best and provides tools and data that can be used in risk-benefit analysis during the regulatory process.

The direct threat of AMR to human health, in terms of mortality and morbidity, particularly in high-income countries, mainly occurs in hospitals and nursing homes among the most vulnerable patients (the young, the sick and the elderly). However, research suggests that everyone carries commensal bacteria that have acquired resistance genes making this a challenge that requires a networking approach. Also, an ageing population and the increasing prevalence of conditions like obesity and diabetes – trends seen worldwide – will cause a significant increase in the number of vulnerable members of society for whom AMR causes the biggest burden in terms of human mortality and morbidity. A trans- European and trans-sector approach is crucial to the successful implementation of this Action. This network has a goal to grow with expertise on this matter, in an effort to bring together different disciplines and stakeholders, in order to be aware of new strategies and products in this fight against AMR.

AMR is tightly linked with the 'OneHealth' concept, which recognizes that human and animal health are inextricably linked by interactions through direct physical contact with farm and companion animals, the food chain, and the environment. Therefore, the only way to regulate the threat of AMR for human health is through the cooperation and multi-disciplinary collaboration of different scientific disciplines and groups within society. AMICI will contribute to this goal by bringing together stakeholders that focus specifically on the use and application of AMC (materials, performance assessment, risk-benefit analysis, and the new cleaning concept) . It will enable the creation of a future perspective of the use of AMC in new cleaning and its effect on AMR.

1.4.2. In relation to existing efforts at European and/or international level

Coordination of the best European research resources and capabilities will form the necessary critical mass and develop the most advanced scientific approaches to tackle AMR, reversing its increasing trend, and leading to the sustainable use of antibiotics and treatments for infectious diseases. In this context, the networking efforts of AMICI provide an important link to the EC's Joint Programming Initiative (JPI) on AMR. This connection will support the JPI in their definition, development and implementation of a common strategic research agenda that individual Member States are not capable of handling independently. The JPI on AMR will develop integrated approaches to pursue unique, world-class research on AMR that will be translated into new prevention and intervention strategies that improve the public health and the wellbeing of populations, and deliver economic and societal benefits throughout Europe and beyond. AMICI, as one of the networks bringing together different stakeholders and will contribute to an important element of the mission of the JPI AMR: to connect to and collaborate with the different stakeholders involved in its mission.

Some of the JPI AMR recommendations are pivotal to the AMICI Action. For example, development and implementation of interventions to prevent colonization, infection and transmission of resistant bacteria by hospitalised patients. Research on the effectiveness of intervention strategies and how they can most effectively be implemented is also required. Furthermore, political and societal awareness on the threat of AMR is crucial to stimulate the implementation of measures to fight the misuse of antibiotics and to stimulate innovation. Knowledge transfer and intensive collaborations

between scientists and policy makers is important for the successful adaptation or adoption of measures that have impact on reducing AMR, have social support and are cost effective.

Many efforts to reduce AMR have been initiated, are ongoing and have been concluded. However many of these have been proven to be only partially sufficient. In order to succeed, a holistic approach is needed (Communication from the Commission to the European Parliament and the Council - Action plan against the rising threats from Antimicrobial Resistance). AMR is a major European and global societal problem, involving many different sectors e.g. medicine, veterinary medicine, animal husbandry, agriculture, environment and trade. It cannot be tackled successfully through isolated, sectoral efforts. Food and direct contact with animals may serve as a vehicle for the transmission of AMR from animals to humans emphasizing the link between human and veterinary medicine in line with the "OneHealth" initiative. The fact that resistance may spread from country to country when people and animals travel or when food, feed and other possible vehicles of AMR are traded, stresses the need for coordinated efforts across borders. The AMICI network addresses key actions as formulated by the EC, for a successful fight against AMR including the prevention of microbial infections and their spread through the sustainable introduction of AMC and new cleaning.
We anticipate that AMICI will be an innovative, out-of-the-box network that will challenge classic approaches in this field, such as new antibiotic development, thereby challenging older concepts and sectoral thinking and pave the way for innovative approaches, such as introduction of AMC and new cleaning. The make-up of the consortium , representing the entire value chain in healthcare, has the power to introduce new concepts into existing structures in hygiene, microbial resistance and cleaning-disinfection.

AMICI has contacted other COST Actions, such as iPromedai, to explore how AMICI can benefit from the experiences and results with respect to combatting device-associated infections and the challenges they face in bringing together clinics, engineering, pharmacology and microbiology. But also to evaluate if and how the work from AMICI can feed into the iPromedai network. Similar efforts have been made with FP7 projects such as PARCIVAL, CuViTo, SelfClean and AMSCOPPER.

2. IMPACT

2.1. Expected Impact

2.1.1. Short-term and long-term scientific, technological, and/or socioeconomic impacts

The Action is expected to have an impact in various areas. Most importantly, the research, development and innovations to be accomplished with the networking support of AMICI will result in a decrease of HCAI's, leading to fewer infected patients and a subsequent reduction of direct and indirect healthcare costs. A large portion of the deaths, resulting from HCAI's is due to multi-drug resistant bacteria. AMICI focuses on fighting multi-drug resistant bacteria via coating of non-invasive materials and surfaces, such as operating rooms and tables, door handles, clothings, the interior of ambulances etc. The expected impact of the COST AMICI Action is:

- Development of ‘Safe by Design’ approaches leading to sustainable, innovative and effective antimicrobial materials and products leading to an increased competitiveness of European industries in innovative antimicrobial materials and products.
- Reduction in the spread of multi-drug resistant bacteria and HealthCare Associated Infections
- Sustainable application of the ‘new cleaning’ approach in healthcare.
- Reduction of direct and indirect healthcare costs.
- Reduction of costs for cleaning as well as indirect costs of environmental emissions in healthcare and possibly other sectors like food production, packaging and distribution.

Impacts WG1: database of active ingredients and substrates for best-practices of AMC in healthcare; use of (European) networks to obtain up-to-date input from nanotechnology into this application field; AMC framework for development of safe products – satisfactory to biocide regulation, without harmful environmental emissions (Safe by Design)
Impacts WG2: innovative test methods for determination of field test efficacy; comparison of the antimicrobial activity of different coatings/materials; prediction of AMC efficacy in different applications and healthcare settings; inventory of field studies where AMC have been used in different healthcare settings; guidelines for selection and application of AMC in the healthcare sector; prediction of effectiveness of AMCs in preventing the spread of infections in the healthcare.
Impacts WG3: responsible for introduction of AMCs in healthcare and other sectors; contribution to the setup/validation of testing methods to evaluate (eco)toxicity; understanding in bioaccumulation and retention of relevant nanoparticles in relevant environmental compartments; open-access to knowledge on the potential impact of (nano)-coating induced bacterial resistance.
Impacts WG4: safe, innovative, and durable cleaning methods using AMC containing sustainable and non-hazardous ingredients; comparison of the developed AMC-based cleaning systems with regard to safety, efficacy, sustainability and durability with the systems frequently used in healthcare; dissemination of innovations in new cleaning approaches in support of policy makers to increase introduction of them in healthcare settings.
Impacts WG5: effective dissemination of the Action findings and results; well-informed network of stakeholders and experts in the field of AMC in healthcare.

2.2. Measures to Maximise Impact

2.2.1. Plan for involving the most relevant stakeholders

Crucial stakeholders to the Action include governments/ intergovernmental organisations involved in health care, regulators, suppliers, academic and industrial institutions and associations, other relevant EU programmes – all on a national and European level. Engaging with stakeholders is essential in meeting the objectives of the COST AMICI Action and ultimately benefit to society. The AMICI Action will be introduced in order to build its reputation, develop long-term relationships and help understand stakeholder/users concerns and expectations. The Action seeks to actively engage stakeholders to create an environment that is supportive of the Actions objectives. The variety of network relationships means an engagement in different ways, depending on the nature of the interest, the relevance to Action objectives and the most practical way to meet stakeholders/users specific needs and expectations. The Action will operate via traditional routes on a personal level, inviting stakeholders to internal and external events and looking into crowd-sourcing opportunities, integrating relevant stakeholders at the right stages of the AMICI project. However, the focus in the stakeholder approach lies in the the development activities online (website, social media). The consortium will monitor the outcomes of stakeholder relationships and make best use of the online platforms. An important aspect in stakeholder engagement is to manage the expectations of internal and external stakeholders which should be based on trust, respect and transparency.

2.2.2. Dissemination and/or Exploitation Plan

The D&E plan will be executed within WG5 and will provide the appropriate communication tools to support promotion and exploitation of the project as a whole, specific WG components as needed, and the overall importance/progress of AMC. Additionally, the D&E plan will develop and implement the tools required for dissemination of intermediate project results as well as the recommendations and results of the consortium at the end of the project. Also, making the connection to existing AMC initiatives is part of the D&E plan as this will create synergies with the Action's efforts and support maximum exploitation of results. The main elements of the D&E plan are aimed at:

- ensuring active engagement of a wide and relevant stakeholder forum

- ensuring wide dissemination of the project's progress and results to all potential interested parties and share the best practices of the project
- warranting optimal exploitation of project results
- raise public awareness about the project results and receive valuable feedback
- liaison and leverage with other AMC initiatives

The audience targeted for the D&E plan will consist of the stakeholders as described in the previous section, but the general public will be reached as well. AMICI aims to interact with different existing communities, professional organizations, industrial forums and special-interest groups in order to achieve targeted and effective impact and to gather their feedback.

As outlined in WG5, dissemination and communication tools to be used will range from social media and web based communication, to scientific articles in relevant journals, to targeted communication campaigns via electronic and print media. A dedicated project website will be created to include overall project and individual partner information, scope of the project, outline of main steps, etc. It will have links to appropriate stakeholder and other relevant AMC web sources. Active e-mail campaigns will be undertaken, specifically at the start of the project, also to extend invitations to join the AMICI Action, and repeated as needed throughout the project. Communication in support of the Action and events will include materials like posters, tryptique, brochures, etc. These will be distributed to places where a high concentration of interested parties can be expected such as AMC conferences, etc. The Action will also issue factsheets to report on results and recommendations.

2.3. Potential for Innovation versus Risk Level

2.3.1. Potential for scientific, technological and/or socioeconomic innovation breakthroughs

The ultimate breakthrough the AMICI consortium will aim at is a substantial decline in number of patients with HCAI, a reduction in morbidity and mortality due to HCAI and a decrease in newly developed multi-resistent microorganisms. This will lead to a considerable reduction in costs attributable to HCAI. The implementation of the new cleaning concept is foreseen to further reduce costs compared to traditional cleaning and hygiene aspects. Moreover, application of Safe-by-Design AMC in healthcare will have lower negative impact on the environment as frequently used chemical disinfectants. An increased competitiveness of European industries in innovative antimicrobial materials and products can be expected.

3. IMPLEMENTATION

3.1. Description of the Work Plan

3.1.1. Description of Working Groups – Provide for each WG the Objectives, Tasks, Milestones and Deliverables

WG1: Antimicrobial materials Safe by Design

Objectives: When using AMC, different chemical and physical strategies can be used as opportunities to fight bacterial contamination. As a first crucial factor, the substrate and the function of the product or surface (e.g. clothing, gloves, doors, tables) must be considered. For example, the same material on a different surface may cause a massive release of biocides, such as silver ions, due to incomplete binding or may influence the dose of UV radiation required to activate materials incorporated into the coating. WG1 aims to reach a conceptual understanding of the mechanisms

and construction of an active and sustainable coating, so that current coatings can be adapted and new coatings developed to meet ECHA demands before September 2016.

Tasks: The WG1 members will address the Safe-by-Design challenges through their expertise in the field and technological achievement in running non-COST funded projects by, for example:

- disclosing up-to-date knowledge of nanotechnology and biotechnology to be used in construction and synthesis of coatings;
- designing coatings that maintain sufficient killing efficacy of bacteria at low release of the active ingredient;
- designing coatings that become active when needed (triggered by contamination) and have little activity when no deposition is apparent;
- constructing coatings on a Safe-by-Design principle that enables sustainable easy cleaning at low cost and minimal release of active ingredient;
- designing coatings that function under actual conditions of use.

Deliverables/Milestones

- Database combining active ingredients and substrates to give guidance to best-practices of use of combinations of AMC in healthcare.
- Exchange of unpublished information between Action members on AMC and their applications; collect information of advantages and disadvantages of different designed materials and coatings to enable development of safe products that will pass biocide regulation and not cause environmental emissions upon long-term use in both healthcare and the food sector (Safe-by-Design).
- Opinion paper on safe-by-design approaches in developing and application of AMC.
- Training schools and STSM on best practices on coating development and application in healthcare for suppliers.

WG2: Performance assessment (lab – field – benchmark)

Objectives: Current and new AMCs will only enter the healthcare market if their efficacy is shown in appropriate field testing and when they comply with the new biocide regulation. Testing AMCs in a healthcare environment has ethical and practical issues, and it is also expected that the site of intervention (textiles, cleaning, surfaces, clothing) will have a strong influence on the total ecosystem in a care environment. Therefore it is important to develop lab – and field - benchmark tests that can help predict the efficacy of coating components as part of the cleaning processes used in healthcare. In addition, it is necessary to predict the overall efficiency of such interventions on bacterial contamination in the hospital and care environment. Even though the efficacy and efficiency may be shown and predicted, the perception of professionals in healthcare favours currently disinfection before use, rather than to preventive killing upon deposition by AMCs. Also, it is anticipated that the reinforcement of the new biocide regulation will cause a huge reduction of available coatings on the market. This combination of events calls for guidelines by which hospitals as well as suppliers of AMC can create safe coatings and safe applications in healthcare. Part of such guidelines should be simple, quick and reliable tests that can be used to evaluate the efficacy of coatings, application and their durability.

Tasks: The action members in WG2 will address these challenges through their expertise in the field and experience gained from running and completed non-COST funded projects by, for example:

- designing benchmark tests that predict the effect of AMC in healthcare environments;
- predicting the efficiency of AMC when implemented at different levels in the healthcare organization;
- evaluating and comparing antimicrobial activity in a laboratory setting as well as in field tests;

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- developing and communicating guidelines that can be used by suppliers and users in healthcare to select safe and effective applications.

Deliverables/Milestones
- Exchange of unpublished information (best-practices) between Action members on lab and field tests to measure efficacy of AMC
- STSM and Training school on performance assessment of AMC
- Design benchmark tests to predict the effect of AMC in healthcare.
- Publication of Guidelines Assembling multi-aspect test method(s) to assess the performance of AMC.

WG3: Adverse effects/Risk-Benefit analysis

Objectives: The introduction of (nano)-coatings with new active components (e.g. nanosilver) along with different methods for cleaning (WG4) will cause a change in the emission of toxic agents into the environment. Active ingredients will slowly enter the ecosystem and cause exposure of human, livestock and microorganisms to low concentrations of different agents. These agents (e.g. AgNP, Ag^+, CuNP, TiO_2) may cause adverse effects on organisms living in specific water and soil compartments. In addition, the slow infusion of active ingredients may induce AMR that differs from current antibiotic driven mechanisms. The widespread introduction of such coatings therefore needs to be subjected to risk-benefit analyses. WG3 will focus on (eco)toxicological risks and the possible induction of AMR resulting from the use of AMC.

Tasks: The members of WG3 and the network will:
- make an inventory of current know-how of coating associated nanoparticles to the ecosystem, partly by connecting to current large testing programs NanoMILE, NanoREG and national projects such as UMSICHT (Germany);
- draw attention to the fact that AMC may also induce resistance, and separate facts from fiction;
- evaluate and compare the possible development of AMR against (nano)-coatings;
- convince regulatory bodies and analytical services to develop methods to determine nanoparticle distribution in the ecosystem and estimate the long-term degradation of components;
- assist suppliers of coatings in the development of 'Safe by Design' coatings based on knowledge of adverse effects.

Deliverables/Milestones
- Use of AMC in healthcare: a risk-benefit analysis based on selected applications.
- Inventory/review on current know-how of impact of AMC on ecosystems.
- Recommendations on further development and application of AMC on toxicology and AMR.
- Recommendations for manufacturing and application: a guideline for suppliers and distributors.
- Expert statement on further research and policy with regard to prevention of antimicrobial resistance.
- STSM on risk-benefit in the AMC context
- Convince regulatory bodies and analytical services to develop methods to determine NP distribution in the ecosystem and estimate the long-term degradation of components.

WG4: The New Cleaning

Objectives: For decades now cleaning in sectors like healthcare has been performed in a rather conservative way. The use of all known detergents and disinfectants with all the well-known

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ingredients has hardly changed. There have been no real innovations. The most promising was the use of less dangerous (= less acute toxicity for humans) products. However, in the meantime the world faces a changing pollution climate with a strong increase in organic pollution caused by the traffic and new multi-resistant bacteria, algae and moulds. Nowadays the common detergents and disinfectants are no longer sufficient to ensure a healthy environment for people and livestock. WG4 aims to investigate new methods of effective cleaning in addition to the use of AMCs to ensure a safe and more hygienic future.

Tasks: The members of WG4 and the network will:

- Inform healthcare professionals of the benefits and the need to change approaches to cleaning, based on facts and figures;
  - bring together “OneHealth” and “Cradle2Cradle” in cleaning systems.
  - Compare AMC based cleaning systems regarding safety, efficacy, sustainability and durability to the frequently used systems in healthcare.

Deliverables / Milestones

- Comparison of AMC based cleaning systems regarding safety, efficacy, sustainability and durability to the frequently used systems in healthcare.
- Guidelines on new cleaning procedures for cleaning industries in healthcare.
- Training school for hospital hygienists on hygiene evaluation after introduction of the new cleaning methods

WG5: Communication and dissemination

Objectives: To succeed in the determined objectives and deliverables, communication between Action members and other stakeholders is extremely important. Dissemination of knowledge that has been gathered and developed by Action members is crucial to achieve the Action goals, such as increased application of the AMC along with the new cleaning approach in healthcare. Therefore, a separate working group will be established to coordinate communication and dissemination of findings, guidelines and test methods. AMCs are a new phenomenon in nanotechnology solutions for healthcare. Potential users have little knowledge of the possibilities. The effect and impact of these innovations needs to be communicated to pave the way for the introduction of novel cleaning methods in the healthcare sector. At the same time, regulatory aspects need to be addressed and a risk-benefit analysis on the use of (nano)-coatings in healthcare is required.

Tasks: The members of WG5 will:

- raise awareness on the impact of AMC in healthcare;
- create and facilitate inspiring, efficient and transparent communications channels;
- build and maintain a high quality stakeholder and expert network/ database for the purposes of information exchange and aligning cooperation (starting by collecting personal business relations from Action members to continuously expand this with new contacts).

Means:

- A website to introduce the topic, the Action member organizations and the network; to reach out and to inform about the Action WG’s progress and plans - content by web manager and by all Working Groups.
- E-mails and newsletters to Action members and to the network/database
- Social media (Twitter/LinkedIn) to enhance distribution of news items (find followers in healthcare organizations and other related nanotechnology and health initiatives) - content by web manager and by all Working Groups.
- Distribute news items on websites of Action member organizations
- Join online health, cleaning and facility management professionals forums

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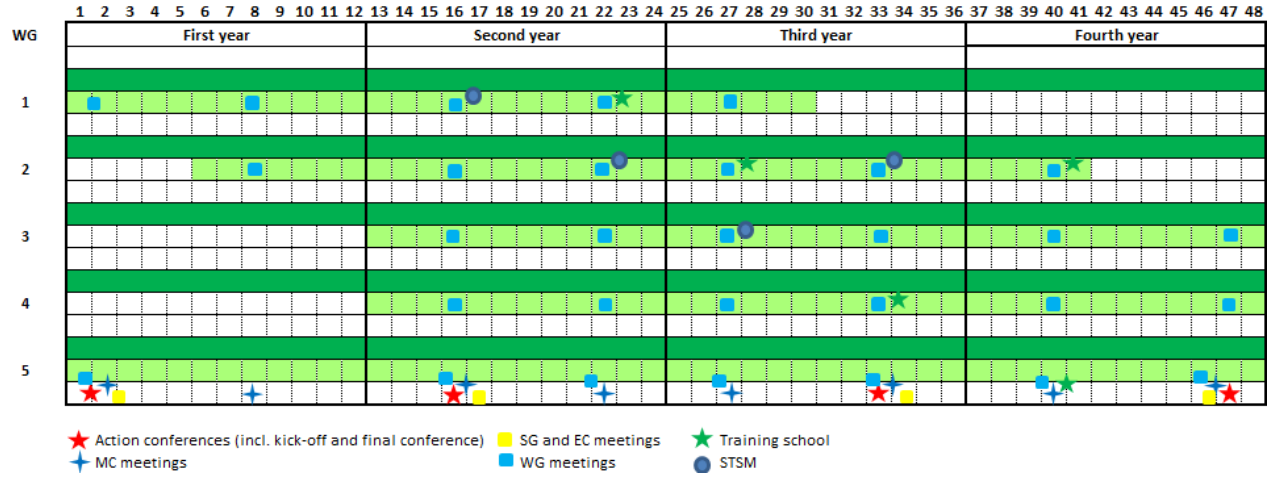
- Join online patient/consumer forums
- Action annual conferences where Action members, stakeholders and experts will exchange visions, knowledge and information (a kick-off event; a mid-term event, a final event
- Participate in conferences of third parties
- Distribute news items through online communications channels of the European Commission or programmes funded by the EC
- Track the scientific publications from the Actions and their impact.

Deliverables/Milestones

- Project website
- Database of experts in the field
- Participation in meetings / events of other networks and stakeholders (e.g. iPROMEDAI, PARCIVAL, ICAR International Conference on Antimicrobial Research)
- Mid-term Conference, Final Conference: exchange of information and dissemination of results
- Involvement of Framework Program policy makers to mid-term and final action conferences
- Expansion of Action network with key stakeholders
- exchange of Early Career Investigators between institutes of different countries and between knowlege institutes and industry

3.1.2. GANTT Diagram



3.1.3. Risk and Contingency Plans

A number of risks can be defined. As is the case for most large-scale projects, there is a risk of partners being unable to commit to their duties. AMICI has already addressed this challenge by involving participants as much as possible in the preparation of the Action, thus ensuring maximum commitment to the actual Action implementation. Additionally, the consortium is sufficiently balanced for other partners to take over any duties that can no longer be carried out by the partner they were originally assigned to. A lack of coordination between interdependent activities may cause delays in the project implementation. WG leaders will be responsible for supervising work progress, coordinating activities and where necessary, make adjustments. The MC will play a monitoring role in this process as well.

At a more scientific level, the potential benefits and widespread application of new antimicrobial projects are as yet unknown to a certain extent. The Action has dedicated a separate WG to identifying potential risks with respect to possible adverse effects that may hamper a widespread

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application. Also, attention is given to regulatory aspects by including research on the new Biocide Regulation.

Transfer of knowledge to the clinical setting is an actual concern. To deal with this issue, AMICI has involved several hospitals as Action partner to obtain sufficient commitment but also to involve them as active partners in the testing and implementation of results and applications. Also, several research partners already have close contacts in healthcare.

3.2. Management structures and procedures

The organisation of the Action has been designed to match the comprehensiveness and structure of the network – at the same time, respecting COST rules. The lead partner is well equipped to coordinate and implement the Action, supported by various internal organisational structures (scientific team, secretariat, financial office). The standard COST management procedures will be followed, including the appointment of a Management Committee (MC) – to be nominated by COST National Coordinators, a Steering Group (SG), an Evaluation Committee (EC), five Working Groups (WGs) and a Dissemination Manager.

Tasks of the Management Committee (MC) include:

- Appointment of SG members
- Planning of MC, SG, EC and scientific meetings; organising scientific networking/ dissemination events (see GANTT diagram for the meeting schedule)
- Monitoring the Action progress, including WG plans, activities, deliverables and milestones – in close consultation with the SG
- Where necessary, taking corrective action to ensure a successful Action implementation
- Wide promotion and dissemination of Action activities and deliverables
- Appropriate allocation and use of COST funding, aimed at a successful project implementation
- Liaising with internal and external stakeholders, experts and platforms in the field; reporting to, and liaising with, the COST Secretariat
- Monitoring gender balance and adequate early-stage researcher participation

A Steering Group (SG) will be created to provide continuous scientific guidance and direction to the Action. The SG will be briefed on scientific and networking progress and will provide input on (external) developments in the field. Based on SG contributions, the MC will translate this input into the Action's further progress. The SG will function at the same time as a basis for the Evaluation Committee (EC) – to be expanded by (external) stakeholders. The EC will monitor and evaluate project results throughout the project, among others by attending at least one Action event per year, by providing feedback and advice on the Action website, and by interacting with the Dissemination Manager. The Dissemination Manager (DM) will initiate and coordinate Action efforts related to the distribution of results, including website setup and management, identification and utilisation of relevant channels for dissemination of Action results (publications, radio/TV channels, events, etc.). The main 'mission' of the DM is to achieve maximum visibility and contribute to a great impact of the Action's activities and results.

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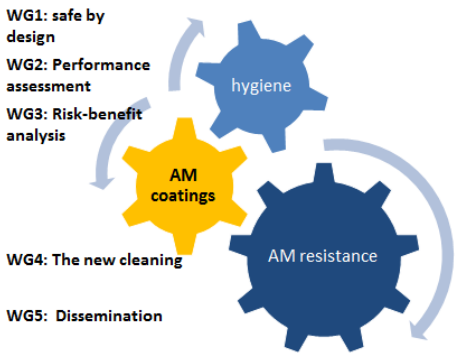

Figure 2: The WGs in relation to the general model which is the basis for the challenges in this program

The WG meetings will be held at the same time and in the same location to maximise cross-fertilisation. Dedicated WG meetings will focus on stimulating the exchange of ideas between institutes and individual scientists, thus building on complementary knowledge and creating new synergies. The Chair and Deputy Chair, to be appointed preferably from two different network partners, will:
* Plan and chair the WG meetings, coordinate and monitor scientific activities
* Promote and help organize WG products and deliverables (STSMs, reports, handbooks, papers,..)
* Participate in, and report to, MC meetings

Participating early-career investigators, already included in the Action as well as new participants, will be involved in the practical and content organisation of WG meetings as much as possible. Two representatives from the Action will be appointed by the MC to coordinate liaison actions with existing programmes, projects and activities, and avoid overlap. Such liaising will include, among others, invitations to participate in meetings and events, open requests to provide input, and inclusion in mailing lists to distribute results.

All meetings, workshops and short-term scientific missions will be organised in conjunction with teaching and education opportunities by the host. Locations will be chosen in the vicinity of highly ambitious pilot areas for materials development or application as catalyst to facilitate and further intensify discussions.

3.3. Network as a whole

The initial Action consortium consists of 16 knowledge institutes and 7 industrial partners, from 11 different European (associated) countries. Fundamental to achieving the individual WG goals as well as the overall Action objectives, these partners represent the necessary expertise in the fields of microbiology, nanotechnology, biotechnology, toxicology, cleaning technology, benchmarking / (field) testing, innovation and communication. A lack of interaction and coordination between sectors and (scientific) fields, the limited availability of information on issues such as AMC effects and performance assessment, as well as the need for new AMC solutions in different fields, has rendered the available knowledge related to AMC fragmented and thus insufficiently effective. By involving these specific partners to collaborate in the above-mentioned fields and sectors, new and existing knowledge related to AMC will be combined, integrated and further exploited. Partners have been carefully selected, based on a lifecycle approach to the AMR challenge, to achieve maximum results without creating overlap and by explicitly bridging existing gaps. Their complementarity in expertise on materials design and development, performance assessment, cleaning methods and communication and dissemination to all stakeholders will create an environment conducive to fruitful collaborations and maximum synergy.

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