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TACKLING ANTIMICROBIAL RESISTANCE IN EUROPE

The discovery of antibiotics against bacterial infections and vaccines to prevent infectious diseases is among the most important public health landmarks in the 20th century. However, the issue of antimicrobial resistance (AMR) is one the greatest challenges facing societies around the world in the 21 century. If the approaches to using, developing and marketing antibiotics do not change radically and rapidly or, alternatively, new vaccines are not developed to close the gap, human as well as animal health may return to a situation where even small infections that are considered harmless today could lead to millions of deaths world-wide.

Danish stakeholders are very active with respect to scientific research in diagnostics for infectious diseases and new antibiotic targets, experimental drugs and alternatives to antimicrobials with different effects and treatment strategies than antibiotics on the market today. Additionally, Danish interdisciplinary research can contribute to understanding, describing and predicting transmission pathways and developing solutions to curb further spreading of AMR transmission through the connecting continua of food & feed production, human and clinical consumption, and environment. Equally, Denmark has a long tradition for developing and producing vaccines.

Based on world leading science in disciplines such as microbiology, immunology, ecology vaccinology, epidemiology and chemical biology we are keen to contribute our input to the forthcoming EU action plan on antimicrobial resistance which the European Commission is expected to publish in 2017.

The EU action plan is expected to include the following strategic pillars:

- Support Member States and making the EU a best-practice region on AMR
- Boost research, development and innovation against AMR
- Shape the global agenda on AMR

RECOMMENDATIONS

In particular we contribute to pillar 2 on boosting research, development and innovation to tackle the problems with AMR. We strongly support continued investments in collaborative research funded by instruments such as the Joint Programming Initiative on AMR coordinated by national funding agencies in the Member States, the public-private partnership programme initiated through IMI as well as funding through the EU framework programmes for research and innovation.

We recommend a holistic and interdisciplinary research strategy that combines tested and validated methods with new innovative approaches. The research should go hand in hand with changing legal requirements on clinical trials and patent requirements stimulating the implementation of practical solutions and products at global level. The OneHealth approach is an

example of a holistic programme. We recommend advocate continuous monitoring, updated diagnostics and effective national and global control of antibiotic use in health care as well as in agriculture including pork, poultry and other animal production, aquaculture, plant production and in relation to waste water. We advocate explicit consideration of how antimicrobial resistance genes (ARG) flow across and between the following different global compartments and how each should be monitored and targeted as barrier for further antimicrobial resistance genes dissemination: animal health, human health, food production, and human and animal waste dissemination, and environment. Initiatives to support and enable identification of novel antibiotic targets and development of a new breed of antibiotics to expand our current assortment are highly needed.

We recommend investments in basic, strategic and applied/industrial research focusing on:

- Prevention of infection and rationale use of antibiotics
- Transmission of AMR and environmental factors
- Diagnostics
- Vaccines
- Discovery and development of new antibiotics and alternative treatment strategies
- Monitoring and predictive
- New financial models and health care practices

Under these headlines we seek to describe the main knowledge gaps relating to antimicrobial resistance and how research and innovation at EU level should contribute to close the gaps. We also provide 2-3 contact persons for each headline. The institutions contributing to this input include the University of Copenhagen, Technical University of Denmark and the Capital Region of Denmark. Additionally, it has close links with the forthcoming national research agenda which is drafted by the Ministry of Education and Research in Denmark.

PREVENTION OF INFECTIONS AND RATIONAL USE OF ANTIBIOTICS

When it comes to investments in research and development preventive interventions and surveillance systems are generally neglected compared to investments in drug development and medical treatment. Prevention is however a very important part of addressing AMR. In human health some of the most vulnerable groups are hospitalized patients that have gone through e.g. surgery or other medical treatment. The hospital is often considered a “hub” for transmitting bacterial infections. Therefore, there is a strong need for designing and testing interventions that prevent the type of infections that can lead to resistance. It should include training and education regarding cleaning and hygiene as well as the use of devices, procedures and biocides which can reduce the spread of infections. Another issue is to detect whether resistance to cleaning and disinfection products contribute to spreading AMR and to develop new concepts for cleaning and disinfection. We also need more knowledge on the route of pathogens and how they enter the hospital and on which part of the patient is colonized first (the skin, the gut, the airways etc.), how pathogens develop further and how resistance is transmitted. Other studies indicate that AMR mainly develops outside the hospitals and transmit globally. This emphasizes the need for improved data on the occurrence and transmission of AMR within and between settings and reservoirs and over time.

This type of knowledge is particularly important to develop more effective interventions which reduce hospital acquired infections at a minimal cost. Additionally such knowledge can lead to early identification of patients with increased risk of infection and thereby a more targeted and effective prevention programme.

Most human consumption of antimicrobial agents takes place in the community (up to 90%). Thus, prevention of community acquired infectious might be even more important than hospital acquired. Preventive measures could focus on community transmission routes such as day-care institutions, schools etc. and implementation of hygienic barriers and vaccination.

Similar knowledge gaps are experienced in relation to animal husbandry. Animal production with no or limited use of antimicrobials requires efficient health management, including vaccination strategies and feed optimization combined with improved management and hygiene measures. There is a need for more knowledge on how to clean and disinfect stables and barns efficiently combined with biosecurity measures to prevent spread of pathogens inside farms between sections. The exposure through different parts of the food chain should also be quantified to target most cost-effective interventions.

In addition to prevention of infections within hospitals, in farms and in the community collaborative research should develop interventions to prevent the spread of new and re-emerging pathogens from outside and within Europe. Pathogens such as tuberculosis, multiple resistant gram-negative strains etc., may enter Europe through travelling, refugees and migrants where as other types of pathogens can enter through food or animal feed. Developing and testing interventions in this area require collaborative research involving different scientific disciplines and multiple stakeholders.

Antibiotic stewardship is needed at all levels, but a better knowledge base is urgently needed to facilitate are more rational approach to using antibiotics. Use of antibiotics is the key selection pressure for the development of AMR. Because of the relative lack of side effects, antibiotics are used even when the clinical benefit is marginal or uncertain. Overuse is common in all disciplines of medicine but the major groups are small children, patients with chronic or acute severe illness, and older people. Large scale, pragmatic clinical trials are needed to define safe levels of reduced use of antibiotics and better understanding of the drivers of overuse is necessary for fair processes in setting priorities.

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TRANSMISSION OF AMR AND ENVIRONMENTAL FACTORS

The public health risk associated with the transmission of non-pathogenic bacteria harboring AMR is not fully understood. The factors and mechanisms that underlie the spread and transmission of AMR determinants in microbial communities need further investigation. An increased focus on basic research in microbial ecology and microbial population genetics is required to understand processes such as horizontal gene transfer and clustering of AMR determinants. Such knowledge is needed to invent novel strategies and AMR resistance management tools. Moreover, there is an urgent need to develop new molecular analytical tools to study AMR in populations which can identify both phenotypic and genotypic resistance on a larger scale.

Food production and waste water management may hold the potential to reduce the spread of antibiotics, mobile genetic elements of AMR and pathogens to and from human/urban compartments, agriculture and the environment. Climate changes; increasing use of surface water resources, increased global demand for meat and urbanization contribute to health related challenges associated with antimicrobial resistance.

Investments in solutions which tackle these challenges at the environmental and food production levels may constitute future European lead markets as such solutions are predicted to be of high demand in other parts of the world. Environmental pollution from e.g. animal manure or waste waters that derive from hospital and farm animal colonization or residential settings – carrying high doses of AMR genes – can constitute a source of selection and spreading of AMR that impacts spread of resistant bacteria in the community and hospitals. However, our knowledge on the links between these different compartments is rudimentary as no useful framework to capture the ecology AMRs across these departments is available.

Assessing the impact on AMR should contribute to improved risk prediction and reduction and novel mitigation strategies that reduce environmental pollution with antibiotics and reduce antibiotic resistant bacteria. Research in the microbiome among humans and animals can also lay the ground for future solutions to mitigate threats from foodborne pathogens or pathogens deriving from food production including manure. Research should improve the understanding of the mechanisms which lead to the development and spread of as well as disappearance of antimicrobial resistance and new pathogens among and between animals and humans and to and from the environment through e.g. water consumption, wastewater discharge, manure land application, and food consumption. Such knowledge should feed into evidence based and effective strategies minimizing further spread of AMR both nationally and internationally.

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DIAGNOSTICS

The rapid development and decreasing cost of molecular methods including genome sequencing should be further developed into new diagnostic methods for both animal and human infections. Molecular methods including bed-site and pen-site methods have the potential to rapidly and precisely diagnose the particular infection. Thereby treatment can better target the pathogen whether it is a virus or a certain type of bacteria. The technologies also have the potential to detect resistance characteristics and thereby can be linked to monitoring of AMR. In addition, using genome sequencing directly on clinical and environmental samples gives the possibility to quantify the prevalence of all resistance genes thereby providing much more detailed information for surveillance and transmission.

New tools are needed to assess the presence of AMR genes as well as the genomic context of the genes (especially the host in which the AMR genes reside) to assess the clinical and ecological relevance of the detection. Improved diagnostic methods, in general, is a corner stone in the fight against AMR since accurate methods will enable a more directed treatment with antimicrobial agents and prevent use in situation where this is not needed. Preferably such methods should be bedside/animal side methods to guide practitioners.

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VACCINES

Basic research to deepen our knowledge about the basic pathogen-host interactions is fundamentally important for the development of new antimicrobial therapies and vaccines. In particular new and improved vaccines are needed against bacterial and viral pathogens. Virus examples are re-emerging infectious diseases such as influenza, MERS, West Nile virus and Blue tongue virus, but also vaccines targeting classical bacterial infections as well as emerging bacteria are likely to become increasingly relevant in the near future.

Interestingly, many viruses possess the potential to be applicable as highly efficient vaccine platforms, and further research into the exploitation of this fact, could drive the development of a new generation of vaccines. Activities favoring vaccines aimed at animals kept in alternative production systems including access to outdoor areas with low biosecurity should be of high priority. Development of broad spectrum vaccines and cost-effective vaccines aimed at livestock production which has the potential to replace antimicrobial treatment should also be prioritized. To reduce antimicrobial usage against primary and secondary (to a primary virus infection) bacterial infections, more research is needed to develop vaccine formulation platforms, which provide safe delivery of antigens in a manner to more efficiently stimulate cell-mediated immune responses in veterinary species. While classical vaccines rely on the principle of induction of a specific adaptive immune response to the vaccine target, an emerging topic in vaccinology is based on the recent appreciation of trained innate immunity. Here an improved immunological functional state is induced to more efficiently combat new infections. Research is needed to investigate this potential as a means to increase health and disease resistance of particularly neonates, where traditional adaptive immunity is difficult to achieve by other means than passive immunization.

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DISCOVERY AND DEVELOPMENT OF NEW ANTIBIOTICS AND ALTERNATIVE TREATMENT STRATEGIES

Antimicrobial drug resistance is constantly developing and spreading over the world and there is an urgent need for novel antimicrobials and treatment options. Some of the most important pathogens belong to the ESKAPE group of microorganisms (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species incl. E. coli*). The causes of resistance are many such as reduced access of drugs due to a modified bacterial envelope or specific changes in the bacterial target. Antimicrobial drug discovery has languished for decades. Therefore, few drugs are under development. It is critical to restart the drug discovery process to find new concepts and new targets resulting in new compounds to fill the clinical need for novel treatment options. Basic science is needed, for instance to develop a deeper understanding of the function and structure of the microbial envelope to identify new targets and to understand how compounds are taken up and transported. There is a need for developing molecular methods to show resistance and strategies to avoid selection for AMR as well as personalised treatment strategies for patients infected with AMR-pathogens. Tuberculosis, HIV, Influenza, hepatitis and infections with ESKAPE pathogens are among the specific diseases that should be addressed urgently at international level.

The development of new chemistry and novel compounds to increase complexity and diversity of the accessible chemical space both relating to targeted and library screening approaches is needed. There is a large number of chemical libraries with millions of different compounds. However, the chemical structures are relatively simple and the chemical diversity is not great enough to effectively identify potential new drugs. One way to gain access to such molecules will require the improvement and development of new technologies to rapidly identify and produce novel candidate compounds that originate from bacteria, fungi, plants or other organisms.

New screening methods that take the whole chemotherapy process into account not only drug-target and drug microbe interactions are warranted.

Novel improved ways of designing pharmacokinetic and pharmacodynamic studies must be developed and implemented to determine dosing regimens that take the potential impact of resistance evolution into account. This is especially important when considering combination of drug therapy due to the increased risk of multi drug resistance evolution.

Moreover, the creation of biofilms often contributes to infections caused by antimicrobial resistant pathogens. Danish research groups hold the potential for the development of novel or non-classical antibiotics that can reduce the ability of pathogens to develop biofilm or alternatively dissolve biofilm when they are formed in the host. These types of antibiotics also hold the potential to reduce the risk of developing resistant infections and reduce the risk of dissemination of mutations.

POTENTIAL PHARMACEUTICAL POSSIBILITIES INCLUDE:

- Focused development of (narrow spectrum) antibiotics optimized for specified resistant microorganisms instead of optimization for broad spectrum compounds in conjunction with better (genetic) diagnostic methods.
- Specific molecular targeting of resistance mechanisms (β–lactamase inhibitors as an example).
- Combined chemotherapy with the current assortment of antibiotics and supporting drugs that enhance their potency e.g. by affecting envelope integrity.
- Development of genomic mining based technologies to rapidly identify and produce novel candidate compounds or modulating activity of existing drugs
- Exploiting anti-virulence/quorum sensing drugs blocking the ability of pathogens to escape the immune system, e.g. via biofilm formation in combination current of antibiotics.
- New bacteria based systems to combat pathogens by infecting them with plasmids and phages. Novel selective gene- edition tools can accelerate technological development to facilitate such systems.

In support of many of the above approaches it is imperative that the regulatory process in drug development is revised to accommodate clinical trials and drug approval relating to narrow spectrum pharmaceuticals that specifically address and tackle the resistance challenge by showing superiority against specific resistant bacterial strains. Likewise the diagnostic approach and methodology to infections must be improved in terms of strain specificity and speed, most likely by including genetic techniques in a personalized medicine approach.

Regarding animal husbandry several promising approaches to address AMR are being investigated. There is a need for more basic knowledge on the mechanisms behind AMR, and to develop tools for more reliable and faster screening methods of promising candidates.

Alternative approaches that may supplement the above therapeutic approaches:

- Vaccines, vaccine platforms and other approaches to manipulate the immune system among humans and animal (*covered separately, see above*)
- Microbial derived products, such as probiotics and phage-derived products
- Non-nutritive phytomedicals including prebiotics
- Immune-related products such as antibodies, peptides and cytokines
- Chemicals including enzymes

More basic knowledge is need regarding the different approaches: mode of action, models for screening of new products, and product optimization. Research should also be targeted at combine two or more of the approaches as possible clinical treatment regimens.

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MONITORING

Europe should push for standardization and further development of monitoring systems to establish a global monitoring and surveillance programme on AMR and the use of antibiotics for humans and animals, including pets and aquaculture world-wide. Technology development in recent years has made it possible to share genomic (bacterial and viral) as well as other relevant data from the health care institutions as well as from society broadly, e.g. sequencing of clinical isolates and metagenomics of sewage, through sensors, monitoring systems, internet of things devices and social networks. The sources of data provide an incredible and rich amount of information. Analyzing these data in combination with explanatory variables, such as travel, trade, climate changes etc. could allow for the development of predictive models to support risk assessment and for the development of population based interventions as well as improved individual treatment of patients. It can feed into the early detection of signs of infectious disease outbreaks including bacterial infections through e.g. food or animals.

In addition to research, there is a need to focus on the cross-sectional and cross-disciplinary establishment of infrastructures and information resources for harmonizing and standardizing detection and surveillance of AMR, interpretation of AMR including predicting phenotypes from genotypes and data sharing for surveillance and comparison at global level.

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NEW FINANCIAL MODELS AND HEALTH CARE PRACTICES

It is a major problem in the fight against AMR that there are limited economic incentives in the market to develop new, efficient types of antibiotics. This type of market failure leads to a situation with potentially significant societal costs. In economic terms it is very important to clarify the magnitude of the societal costs in order to elucidate the potential gains of various types of investments in strategies to counteract AMR. A clearer picture of costs and gains of different strategies will enable a more rational prioritization of efforts, and development of financing strategies to promote the development of innovative solutions. Societal costs are related to monitoring and regulation regimes at the systemic level and diagnosis, treatment and follow-up care at the individual and organizational levels. In a broader perspective it is relevant to look at productivity loss due to illness and premature death as a result of AMR.

Economic analyses are needed to explore the societal costs of AMR, and to clarify the potential gains of different investments for fighting AMR. Furthermore, economic analysis can help understand the micro-level motivations and behavioural patterns that serve to facilitate and hinder AMR. A clear understanding of such behavioral and motivational dimensions can help the efforts to design efficient strategies. It is also a problem that the economic incentives to reduce the use of antibiotics in agricultural production are weak because alternative strategies to control livestock diseases (vaccination, changed feeding, biosecurity) are more costly.

In addition to economic analysis it is highly relevant to conduct policy analysis to identify the positions and incentives of relevant public and private stakeholders. This will facilitate realistic strategic plans and increase the likelihood of efficient implementation of AMR prevention and intervention strategies.

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