Transmission of antimicrobial resistance in different settings: priorities for a Pan-European multidisciplinary approach

Report from the workshop held on Monday 12th October 2015, British Embassy, Berlin

1. Background

The Medical Research Council (MRC) and UK Science and Innovation Network (SIN) are committed to promoting innovation within research, particularly in the area of Antimicrobial Resistance (AMR). A number of initiatives including the UK cross research council initiative[1] and the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)[2] are attempting to address the problem of AMR through the identification of key areas for current and future investment. This includes the transmission of AMR, one of the priority research topics identified in the JPIAMR Strategic Research Agenda[3].

This workshop 'Transmission of antimicrobial resistance in different settings: priorities for a Pan-European multidisciplinary approach' was organised by the MRC and the UK SIN in association with the JPIAMR. The focus of the workshop was to discuss AMR transmission at the genetic, bacterial, animal, human, societal and environmental levels. The 'One Health' concept has acknowledged that multiple disciplines are required to work together to enable the identification and characterisation of the determinants that contribute to the transmission of resistance in and between different reservoirs. This workshop brought together experts from research, policy, healthcare, and industry from across Europe and Canada to determine the research and funding gaps for AMR transmission, and to consider how a multidisciplinary approach at the research/policy interface could support the design of preventive measures to reduce transmission in humans, animals, and the environment.

The workshop was chaired by Professor Bruno Gonzalez-Zorn and was attended by over 60 delegates[4] including the UK Chief Medical Officer, Professor Dame Sally Davies. The day comprised of four short talks which introduced specific topics for discussion: transmission of AMR within a hospital setting, transmission through national health care networks, transmission within the environment and between animals and humans. Two breakout sessions allowed delegates from a range of backgrounds to have more in depth discussions on these topics. Feedback was delivered back to the chair and audience.

[1] http://www.mrc.ac.uk/research/initiatives/antimicrobial-resistance/tackling-amr-a-cross-council-initiative/
[2] http://www.jpiamr.eu/
[3] http://www.jpiamr.eu/wp-content/uploads/2014/05/SRA1_JPIAMR.pdf
[4] http://www.mrc.ac.uk/documents/pdf/tranmission-workshop-final-delegates-handbook-12-10-15/

2. Purpose

The aims of the workshop were:
• To identify the challenges and research gaps that needs to be addressed to prevent further transmission of AMR,
• To encourage networking of researchers across different areas with clinicians and policy makers to form strong multi-disciplinary research teams,
• To provide an opportunity to discuss this topic with a view to informing the development of the upcoming JPIAMR Era Net co-fund call which will be launched in January 2016.

3. Workshop discussions

The short talks highlighted the challenges associated with understanding how AMR is transferred and the interventions that are required to control it in the future. Although the four topics that were presented are traditionally seen as four distinct areas, the presenters emphasised the requirement of working across research areas and disciplines to address the problem of AMR. Professor Mike Sharland discussed transmission of AMR within a hospital setting, stating how little information is available about how pathogens drive transmission of resistance. He discussed that both pathogen and host related factors are involved and acknowledged that improved surveillance systems are essential to understand how outbreaks are controlled.

Professor Hajo Grundmann delivered a presentation on large scale transmission dynamics through national health care systems, which described the impact of the movement of patients through different health care networks. His research showed that most resistance was acquired through mobile genetic elements and stated that an understanding of health care utilisation and referral patterns within hospitals would allow the level of national dissemination of high risk clones to be determined. A comparison was made between the UK and the Netherlands, highlighting the requirement to understand the health systems in different countries to enable appropriate interventions to be designed and implemented.

Professor Liz Wellington provided an insight into the level of AMR that can be detected in the outdoor environment. She detailed the impact of how treated human waste and water (and potentially genes encoding AMR) can be transferred into soil and waterways. Better surveillance systems and longitudinal studies are required to determine the risks of exposure and how these risks can be mitigated. Professor Jaap Waganaar highlighted the issues of AMR in animals. He emphasised the need for evidence based data, the identification of drivers for resistance transfer and risk management options for veterinarian usage of antibiotics. He showed the impact of reducing antibiotic usage in animals on bacterial colonisation, in one study, the level of MRSA carriage in pigs was reduced with a reduction in the use of cephalosporins.

Professor Dame Sally Davies discussed the global problem associated with AMR and the global approach that is being taken to conserve antibiotic effectiveness whilst controlling infection and developing new antibiotics. She also emphasised the successes achieved to date, including the development of a global health security agenda and the One Health action plan that will be in place for all

countries within two years. Dame Sally also detailed how she is working hard to keep AMR on the political agenda.

The breakout sessions entitled 'Identifying the research challenges and opportunities of AMR transmission' and 'Embedding a multidisciplinary approach across countries' gave the delegates an opportunity to have an input into how they believed the problems associated with transmission can be addressed. The feedback is summarised below:

The knowledge gaps

The transmission dynamics between environments are believed to be poorly understood and are likely to differ between bacterial species (particularly Gram negative and Gram positive organisms) with alternative survival mechanisms used in different environments. It was recognised that there is a lack of evidence of AMR transmission in some environments, particularly at the molecular level, although genomic techniques should not be used in isolation. The level of bacterial colonisation and an understanding of how resistance is acquired in different environments are deemed to be unclear. The lack of harmonisation and standardisation of methodology within and between countries makes data comparison between research groups difficult. Better cooperation and coordination between disciplines would improve this.

Health systems and infrastructure differences between countries were raised as issues and as such different problems may exist in different settings requiring tailored solutions. How resistant bacteria are transferred may be the same however the outcome could be very different. A number of key questions were identified on the topics of antibiotic prescribing and outbreak management that require addressing: What is considered to be 'best practice?' What is optimal prescribing of antibiotics? Why are prescribing habits so different across Europe? Are local interventions effective on a global scale? Is it reasonable to screen referred patients? Should healthcare workers be screened? What are the countries that don't report outbreaks doing differently to those that do? How are outbreaks reported and managed? Can the burden of resistance be reduced or controlled? What is the impact of antibiotic use in animals on human health? Do policy changes in veterinary settings have an impact on the environment?

How to address these issues

Better awareness and understanding of what triggers an outbreak is important, longitudinal studies with relevant indicators providing retrospective analysis would aid with this understanding. Although this type of surveillance would be useful, key issues are required to be addressed regarding how the surveillance is structured, sampled and the data competitively analysed and made accessible to the relevant communities. The negative connotations and publicity associated with outbreak notification was also considered to be an issue, one aspect which may be preventing timely reporting. An understanding of how the transmission of some resistant bacterial species, for example, MRSA, has reduced would enable new infection control measures to be developed.

Having sensitive tests available to rapidly screen patients and healthcare workers for bacteria with specific resistance profiles would enable timely identification of a potential problem and allow the necessary restrictions and control measures to be implemented. It is a requirement that this research is

linked to policy. Gaining information on the identity of an infecting organism and the level of bacterial colonisation is believed to be important. This may provide an indication as to whether an outbreak becomes established. A better understanding of the effect of human migration and international travel on population dynamics within the community and hospital setting is required, including both primary and secondary health systems. The consequence of animal and food movement on AMR emergence and spread is largely unknown.

A cost benefit analysis to investigate whether effective infection control can be implemented was considered to be important. The differences regarding human or animal only clones and host specificity were identified as basic research questions that are still unanswered. Successful partnering with other research groups across the world would provide a better global overview and would ensure that the right studies are designed and performed.

Access to information and collaborative working

More visibility of existing data is considered to be important, allowing researchers to learn from past successes and failures and ensure there is no duplication of effort. The mechanism by which information is currently shared (particularly between different disciplines) needs to be improved to allow data to be more accessible. Knowledge, resources (including clinical isolates) and expertise should also be shared across countries. Better surveillance tools and uniform approaches are required to provide real time data and reduce the differences that currently exist between and within countries. The issue of AMR transmission needs to be recognised as a global problem and not thought of as a European issue, boundaries are porous and the dynamics of AMR transmission is complex.

The importance of training and support given to new investigators in the field of AMR was recognised, one approach discussed was to link with more experienced members of the AMR community. A scheme allowing PhD students and/or post-doctoral scientists to 'discipline hop' and spend time in different laboratories would encourage communication between areas. Dedicated PhD programmes specifically focused on AMR would encourage multidisciplinary working. More networking opportunities for example, sandpits and workshops are required to encourage scientists from different backgrounds to meet; this would enable researchers to consider different perspectives, for example, the wider implications of an intervention taken by a clinician or veterinarian. These types of networking events would help in the development of collaborations.

AMR centres of excellence acting as a central repository for information available to all researchers in the AMR community was considered to be a good idea. Rapidly available funding for short pieces of work and more money available for AMR research was also considered to be important. Improving how the AMR community engages with the public was highlighted and the potential of public private partnerships as a source of funding was discussed. A clear understanding of the regulatory frameworks was also considered to be essential to ensure awareness of the barriers that may exist.

Key Conclusions:

- Transmission dynamics between environments are poorly understood
- Lack of harmonization between countries, between

humans/animals/environment makes data comparison difficult
- Differences in health care/animal husbandry systems means that tailored interventions adapted to each country may be necessary
- Knowledge gap in factors determining success of specific clones exists
- Understanding human/animal/food movements and their consequences on AMR is not sufficiently known
- Differences regarding human or animal specific clones are yet to be determined
- Multidisciplinary in training, education, networking and collaboration is required

4. The European Research Area (ERA) Cofund call JPI-EC-AMR

This call will be launched in January 2016 and will support multidisciplinary research groups and consortia to conduct collaborative and complementary studies to unravel the complex dynamics of selection and transmission of antimicrobial resistance and understand the mechanisms that contribute to the spread of resistance. This call is supported by 17 countries of the JPIAMR with a contribution from the European Commission. More information can be found at: http://www.jpiamr.eu/activities/joint-calls/3rd-joint-call-transmission-dynamics/

JPIAMR is dedicated to the 'One Health approach' where multiple disciplines work together in the identification and characterisation of determinants that contribute to the transfer of resistance in and between different reservoirs. Investigating the complex biology and epidemiology of selection and transmission of resistance is crucial in order to design preventive measures to address this public health threat. This is a challenging prospect, that requires new ways of working, and therefore multidisciplinary working is encouraged. The projects and research questions will dictate what disciplines should be involved in each consortium; however a wide range of disciplines beyond microbiologists, for example, behavioral scientists, modelers, bioinformaticians, economists and statisticians should be considered where appropriate. Project endpoints need to be clear and timeframes for technical deliverables defined at the start of the project. All projects should have clear objectives and be suitably project managed and reviewed at specified intervals. More formal scientific reviews by expert panels would ensure that the projects are progressing and any issues are identified early.

For further information please contact:

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Or visit:

MRC - http://www.mrc.ac.uk/research/initiatives/antimicrobial-resistance/

JPIAMR - http://www.jpiamr.eu/

SIN - https://www.gov.uk/government/world/organisations/uk-science-and-innovation-network