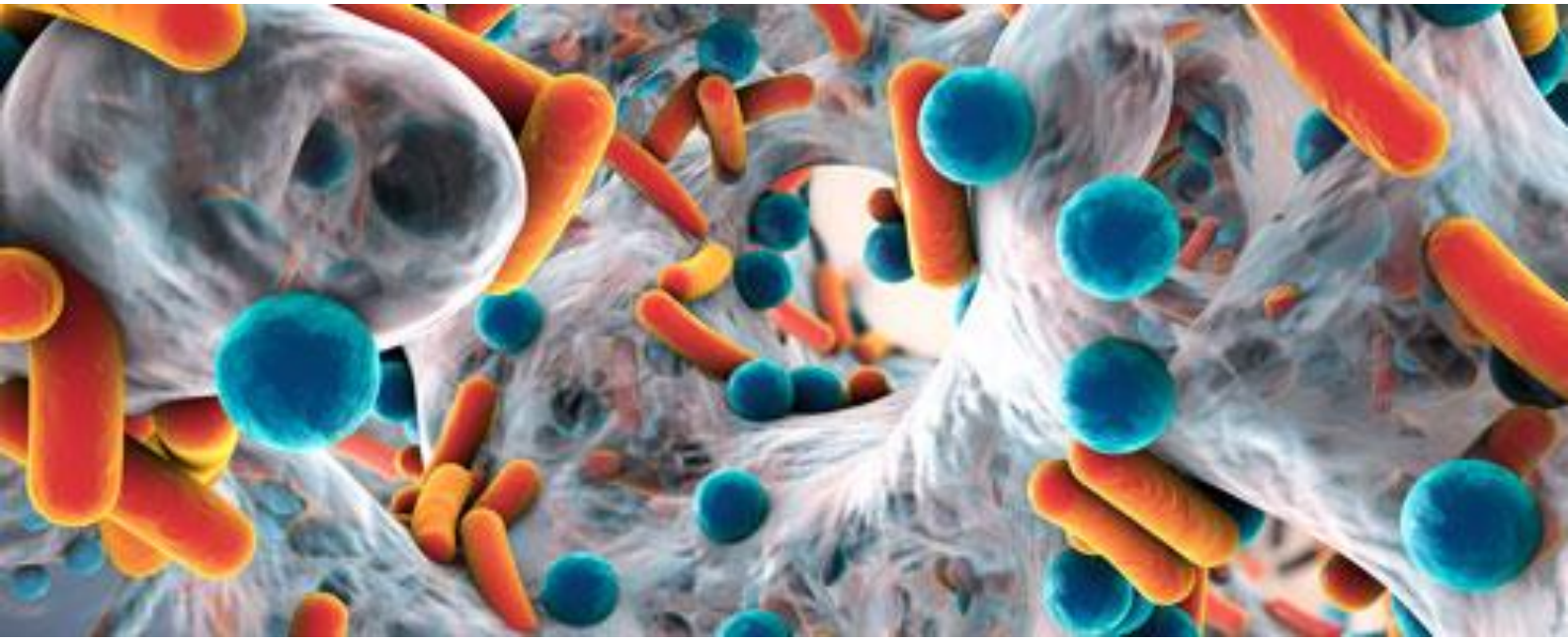

The interplay between AMR surveillance and science

Report of JPIAMR workshop

12.-13. October 2016, The Research Council of Norway, Oslo, Norway

The Research Council of Norway

jpiamr
Joint Programming Initiative on Antimicrobial Resistance

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Abbreviations

AMR; antimicrobial resistance
HiRiCs; high risk clones
JPI; Joint Programming Initiative
SRA; Strategic Research Agenda
ECDC; European Center for Disease Prevention and Control
WHO; World Health Organization
WGS; Whole genome sequencing
ECOFF; ecological cut-off
EQA; external quality assessment
QC; quality control

Introduction

The workshop was hosted by The Research Council of Norway, and convened experts from diverse scientific fields across Europe, Japan and New Zealand. The objectives of the JPIAMR workshop were to identify knowledge gaps in AMR surveillance, and to provide scientific input to the JPIAMR management board for future JPIAMR calls for surveillance research activities. Keynote presentations and group discussions were used to identify knowledge gaps and to suggest areas for future research. The output of the workshop can also serve as a basis for future revision of the JPIAMR Strategic Research Agenda (SRA), Topic C.

Sessions

Scope of the workshop (Gunnar Skov Simonsen)

In this session, the participants were given an introduction to the JPI-mechanism, JPIAMR and the SRA. As yet there has been no JPIAMR call on surveillance. A call can hopefully be launched in 2018. This workshop may help to identify knowledge gaps and future joint actions. Topic C in the SRA includes surveillance on antibiotic use. This was excluded from the discussions in the workshop as it would involve separate methodologies and expert panels. Surveillance is traditionally conducted within the remit of public health, and calls for research activities should not include establishment of surveillance systems. Research activities on AMR surveillance should focus on opportunities for the future with regards to novel technologies, international alignment, surveillance strategies and improvement, and bridging the gap between surveillance in non-human and human health. Science should be used to fill knowledge gaps to optimize surveillance, and surveillance systems should be designed to generate hypotheses and provide data for future scientific projects.

The use of AMR surveillance data in scientific research – opportunities and limitations (Hajo Grundmann on behalf of Liselotte Diaz Högberg)

AMR surveillance at ECDC was presented, including routine surveillance (e.g. EARS-net), point prevalence surveillance and special/focused studies (e.g. EuSCAPE). According to the definition by WHO, surveillance is the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. The routine surveillance in EARS-net is designed to be acceptable and valid. The EARS-net system does not, however, provide data on resistance mechanisms, clonal outbreaks and epidemics, patient risk-factors, or laboratory capacity. Special studies, such as EuSCAPE, can provide better in-depth knowledge, but is restricted in time. Surveillance is restricted by its objective i.e. the operational unit of surveillance (OUS) which represents the quantifiable subject under surveillance. It is of importance to understand how error and bias influences the data. Data quality can be controlled to some extend by standardization, quality assurance of data collection and laboratory procedures, and by clear OUS. Harmonization of susceptibility endpoints such as the agreement to use ECOFFs for human and animal/food data can improve the quality

and be used to explore ecological links between these different environments.

The global transition from phenotypic to genotypic AMR surveillance – how do we get there? (Neil Woodford)

Antimicrobial treatment is usually empiric, and there is a need for fast and accurate methods for antimicrobial susceptibility testing to improve clinical prescribing decisions and antibiotic stewardship. Whole genome sequencing (WGS) provides new opportunities for fast and detailed characterization of bacteria, including the prediction of AMR. WGS is currently being introduced for priority organisms in several centers, and there is a need to provide databases and reference panels that can be interrogated with respect to antimicrobial susceptibility. Due to the diversity of resistance mechanisms in bacteria, validity of AMR prediction using WGS data will differ between bacterial species and antibiotic classes. The evidence base for prediction is constantly growing, and the quality of databases must be guaranteed. Prediction of susceptibility in a phenotypically resistant isolate is considered a very major error. Such errors can have grave consequences for clinical decision making and patient outcomes. However, for AMR surveillance the unequivocal indication of presence or absence of defined resistance genes or resistance mutations for each individual genome gives WGS data a significant advantage over conventional phenotypic methods. Yet, there is a need for standardization, centralization, and curation of databases, and for funding, in order to provide long-term global standards for AMR surveillance based on WGS.

Novel technologies and strategies for surveillance (David Aanensen)

WGS is a powerful tool to characterize bacterial isolates, and provides crucial information about the emergence and spread of bacterial clones and lineages at all geographical scales using simple surveys or surveillance systems. WGS data can be imported into web-based tools to infer genetic and phylogenetic relatedness, and to visualize temporal and spatial distribution of clones. Moreover, online tools can illustrate all contextual

Photo: Workshop participants

epidemiological and clinical information in an intuitive manner when supplemented with metadata which can be collected by surveillance or structured surveys. There is a need for structured sampling of bacterial isolates and epidemiological data to provide for sufficiently detailed datasets. So far WGS analyses have shown their public health value only for repeated structured surveys but not yet for large scale surveillance efforts.

The interplay between surveillance and science to optimize patient management (Group discussion chaired by Hajo Grundmann)

AMR surveillance is defined by objectives reflecting stakeholder demands, whereby maintaining the clinical effectiveness of antibiotic treatment is the final goal. Since stakeholders vary from patients, medical professionals to public health specialists, and politicians all the way to pharmaceutical industry, different surveillance information is required and single surveillance systems may not be able to satisfy all demands. In order to provide the nexus between local, syndrome-based and near real-time surveillance to optimize patient treatment and antibiotic stewardship and large scale population-based surveillance that informs about the magnitude and burden of disease incurred by AMR, open access data platforms combining epidemiological data, phenotypic characteristics and WGS sequence information would allow for rapid interrogation and data retrieval for multipurpose demands not least informing the scientific discourse. This would provide an opportunity where practitioners at all levels would garner the support from evolutionary biologists and vice versa. Breaching the technology gaps especially in LMICs and the interplay between surveillance and science were discussed in terms of science for surveillance, and surveillance for science.

The interplay between surveillance and science to contain non-human AMR reservoirs (Group discussion chaired by Bruno Gonzalez-Zorn)

AMR surveillance of animals differs from that of humans; surveillance is performed on healthy animals, follows a structured sampling, and testing is to a large extent performed by centralized laboratories and with no curative purpose. Despite the robust data on AMR in animals, there is a clear knowledge gap of bacteria and AMR between the sampled animals and the patients in Hospitals. Use of WGS can improve the knowledge of spread of AMR from and within non-human reservoirs, and possible links with human health, but data on the epidemiology and context are needed to realize the full potential of the novel technologies. As for the environment, no surveillance data at all exist regarding AMR. Research is needed to identify the surveillance sites needed to assess the spread of AMR between different ecological niches. International trade and movement of animals and food items is a mechanism for spread of AMR, and warrant surveillance.

The knowledge gaps identified by the two groups are summarized in tables 1 and 2.

Output

Knowledge gaps identified

Surveillance and science are linked. Surveillance can provide data to scientific questions and studies, science and scientific achievements can provide tools to improve surveillance, and surveillance as such can be the object studied by science.

The discussions were not structured to identify knowledge gaps within one of these categories specifically, but on surveillance and science as a whole. The discussions revealed several knowledge gaps and areas on which improved knowledge is needed. The lists of knowledge gaps in table 1 and 2 demonstrate the diversity of areas discussed. However, several knowledge gaps are related, and can be grouped into areas that are briefly described in the following sections.

1. Objectives/purpose of surveillance and surveillance strategies;

Surveillance systems can be designed to answer a set of questions. Ideally, the design of surveillance systems should accomplish the objectives defined by stakeholders. A system intended to rapidly pick up a signal about the occurrence of high risk clones (HiRiCs) or changes in AMR prevalence, analogous to an early warning system, will need to be designed differently than a system to detect shifts in trends over time. The lack of solutions able to reconcile the needs at both ends of this spectrum of data demand was identified as one of the main gaps in the current AMR surveillance landscape. Generic tools are needed to synthetize traditional strategies used for surveillance of AMR in human (case-based, diagnostic approach) and non-human (healthy animals, screening/surveys) reservoirs. Community and hospital case-based approaches are valuable to determine population risks and can inform burden of disease estimates, but the quality and consistency of routinely available data is often not sufficient for the systematic collection and interpretation. Especially in resource-limited settings, health services must be supported by easily accessible communication systems. Usefulness of smartphone technology (E-health) that could be harnessed for this purpose should be explored. Moreover, structured and repeated surveys can be tailored to answer detailed questions by a more extensive data collection. Strategies for surveillance and structured surveys may be explored, in order to describe sustainable and affordable mechanisms of providing data needed for public health and research, in high and low income settings. Optimal strategies should allow for relating data from human and non-human sources, linkage of available data, and for including data on outcome, risk factors and epidemiology/demography and on origin of non-human specimens (food). Strategies may be studied by modeling and network analyses, and by feasibility testing. The development and implementation of surveillance and surveillance strategies may be guided by assessing the overall impact of surveillance on clinical practice, infection control and patient management.

2. Reservoirs, and links between them;

AMR bacteria and genetic elements that confer antibiotic resistance (R-genes) can emerge and accumulate in human and non-human reservoirs. The role of different reservoirs and their impact on health, needs to be better assessed. Routine structured surveys and surveillance of relevant habitats should therefore be harmonized by coherent sampling frames and a comparable data structure. The resistome or microbiome of carriers and reservoirs can be characterized and studied by the use of novel technologies e.g. deep sequencing. Present surveillance systems in individual high-income countries include and integrate resistance data from separate sources to some extent, but the optimal strategy for AMR surveillance within a One Health approach has not been defined. Of

special concern, many studies focus on "proof of principle" for contact between resistance reservoirs but are not designed and / or powered to define direction or extent of transmission. The data generated consequently have limited value for risk assessment, and are not implemented in surveillance systems.

3. Novel technologies;

Widespread implementation of WGS for the characterization of bacterial pathogens offers new opportunities for studies of isolates, microbiomes and resistomes. Evolutionary events that lead to the expansion or decay of HiRiCs can be elucidated and the resulting population dynamics put into the context of human health or its impact on patient management. Furthermore, WGS methodology can be used to identify resistance profiles and clonal profiles of bacterial isolates. The development of these technologies is mainly driven by science. There is a need to improve bioinformatics pipelines to create and maintain freely available (open access) data warehouses where WGS data and metadata can be imported, quality checked and individual isolates put into global context. The question also needs to be addressed, to what extent novel technologies could replace or bypass surveillance approaches based on conventional phenotypic characterization of isolates, and if LMICs should pave the way to leapfrog the current technological divide providing evidence through proof of principle and feasibility investigations.

4. Context, epidemiology and patient outcome and burden of disease;

In order to assess the impact of interventions and the impact of AMR on human health, data on the context, patient outcome and characteristics are needed. Novel technologies could provide characterization of pathogens and bacterial populations. Surveillance is observational, and can only suggest impact of interventions on a population level. However, surveillance could provide a framework to design studies of interventions.

Conclusion

The knowledge gaps that were identified could be amended by scientific development and studies focusing on surveillance as such (science for surveillance); studies on the surveillance tools, surveillance strategies and harmonized sampling frames and the implementation and standardization of novel technologies for surveillance purposes. Several gaps in knowledge can be amended by studies for which routine surveillance and structured surveys are a premise (surveillance for science); studies about reservoirs and their interfaces, and impact of interventions using data from surveillance and structured surveys.

WGS allows a leap forward for surveillance. However, data on the context, on patient outcome and on demographics is needed to amend the knowledge gap on impact of interventions and impact of AMR on human health.

The workshop also identified a need for funding of working groups/networks to improve and maintain surveillance tools nationally and internationally.

Recommendations

The workshop concluded that advanced AMR surveillance is needed for public health purposes for global burden of disease estimates. It is necessary to improve and integrate surveillance strategies for humans, animals and the

environment, but the optimal model to achieve this has not been defined. Novel technologies have the potential to improve AMR surveillance as the integration of detailed genotypic data and relevant epidemiological metadata will expand our understanding about the dynamics of AMR emergence, expansion and decline. However, this potential will not be realized without a solid evidence base including validated systems for the analysis and storage of data. A future JPIAMR call for research on surveillance should take into account the knowledge gaps and priorities identified by the workshop.

Table 1. Knowledge gaps in the AMR interplay between surveillance and science to optimize patient management.

Knowledge gap
Role of different reservoirs of AMR – infected humans, colonizes humans, travelers, migrants, animals, environment; interfaces between different reservoirs and their relative importance - What is the role of different reservoirs, healthy carriers, commensal flora, non-human reservoirs? - What is the significance of AMR in healthy carriers? - How to do surveillance in risk groups e.g. migrants, travellers? - What is the relative importance of different transmission routes?
Population history of AMR bacteria - What are the mechanisms behind the selection, expansion, and decay of AMR clones? - Why do some clones turn into HiRiCs? - What is the link between AMR and virulence and tenacity of clones? - What is the molecular basis of resistance acquisition? - What are the molecular mechanisms behind adaptability of clone to host (human vs. animal)? - How can the success of clones and impact on patient management and clinical outcome be predicted; metagenomic approaches (impact on microbiome)?
Cause and effect chains - What is the impact of interventions on AMR? - What is the impact of deteriorating and ameliorating factors on AMR? - What is the impact of interventions on patient outcomes and burden of disease? - Could surveillance data be linked any better with interventions? - What is attributable impact of AMR on patient outcome? - What is the impact of antibiotic use on AMR? - What is the correlation of AMR phenotype and treatment outcomes? - Correlation between treatment and composition of microbiome in individuals - What is the impact of local and national guidelines for prescribers on AMR? - What is the impact of surveillance on clinical practice, infection control and patient management?
How to improve the capacity for AMR detection - How to optimize surveillance in resource-poor settings: society, economy? - How can capacity of AMR detection be improved globally? - How to optimize feedback of surveillance data locally for action?
Standardization of databases / strain collections - How to utilize new technologies? - How can genomic markers for predicting AMR be identified, validated and implemented for routine analyses? - What is the validity of using subset of resistome on new diagnostics? - How to establish phenotypic/genotypic concordance across multiple bugs/drugs? - How to make software for WGS readily available for use in diagnostic labs? - Harmonization of data and making them accessible to policy makers

AMR; antimicrobial resistance
HiRiCs; high risk clones
WGS; whole genome sequencing

Table 2. Knowledge gaps in the AMR interplay between surveillance and science to to contain non-human AMR reservoirs

Knowledge gap
Role of animals for spread of AMR - How to monitor movement of animals internationally? A system for tracing movement of food production animals is available in EU (TRACES) - How to monitor the movement of companion animals, migratory birds etc? - What is the relative importance of different animals, and what animal movement is strategically most important to monitor? - Are there good resistance data linked to animal antibiotic use data in countries? - What is the importance of trading on spread of AMR? - How can new technology elucidate the role of animal movement on AMR spread?
Role of movement of food for spread of AMR - What is the best strategy to monitor AMR in food? Which food items? Which trading routes? Domestically and internationally, within and outside EU. - What is the relation of AMR spread from animal reservoir to foodstuff? - What is the risk for humans to be colonized with AMR microbes following consumption of contaminated food?
Role of reservoirs; sampling of community, carriage, environment - Sampling for AMR surveillance in humans is mainly from patients. What is the role of animal and environmental reservoirs for AMR on carriage in a healthy human population? - What is the best strategy to monitoring AMR in a healthy population? - How to identify the mechanisms and relative roles of routes for introduction of AMR into the hospital system? - Could monitoring of AMR in sewage systems be used as a proxy for the burden of AMR in humans? - What is the role of AMR in emerging, usually non-pathogenic bacteria? Could ECOFFs be designated for emerging bacteria lacking clinical breakpoints? - What is the role of the context, demography and clinical characteristics, for the spread of AMR from reservoirs? - How can new technology elucidate the role of reservoirs on AMR spread?
Standardization of databases / strain collections / data availability - How can shared databases of metadata (context), epidemiological data, genome data be established and curated? - How can existing databases and sources of information be made available and integrated for research and public health? - How can prediction of AMR from WGS data be established and standardised? - How do we improve and make available the bioinformatic analysis-tools for WGS data? - How can the quality of databases be sustained, what is the role of EQA and QC on the data that is entered in databases?

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ECOFF; ecological cut-off
EQA; external quality assessment
QC; quality control
WGS; whole genome sequencing