FINAL REPORT

UK – Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment

December 2021

GenomeCanada GenomeAlberta UK Research and Innovation Natural Environment Research Coun Medical Research Council Biotechnolog Biological Sci Research Cou AMR One Health Consortium ONE HEALTH at UCalgary

EXECUTIVE SUMMARY

Experts on Antimicrobial Resistance (AMR) from academia, government, and industry were invited to participate in a **UK-Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment** (September 23, 2021) co-hosted by UKRI, Genome Alberta, One Health at UCalgary and the AMR – One Health Consortium. Workshop presentations and breakout sessions were organized into three themes: (1) Antimicrobial Use (AMU) and AMR within reservoirs of AMR, (2) Transmission of AMR between reservoirs of AMR, (3) Use of genomics to improve AMR surveillance. The objective of the workshop was to better understand UK and Canada's research strengths and gaps regarding AMR with a view to identifying future opportunities for bilateral collaborations.

This final report organizes pre-workshop survey findings, workshop presentations and breakout discussions notes recorded into five sections. In section *I. Introduction*, a brief over of AMR is provided along with details on how the workshop was structured. In section *II. UK-Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment*, unique strengths, research gaps and projects (with potential for bilateral collaborations) are reported for each of the three themes. This is followed by two brief sections, *III. Closing Remarks*, and *IV. Next Steps*. Lastly, in section *V. Appendices*, a total of six appendices are included: a) workshop agenda, b) pre-workshop survey questions and UK-Canada synthesis of responses, c) list of workshop attendees, d) workshop presenter biographies, e) workshop presentations – summary notes, f) workshop breakout sessions – summary notes, by theme.

THEME 1 Highlights. The UK and Canada agri-systems, natural environments and cultures have unique features that may either encourage or inhibit AMU and AMR within reservoirs of AMR. These features include differences in farm number, farm size, cropland, livestock inventories and management systems. In both the UK and Canada, the regulatory landscape is often complicated by the fact that the responsibility for lawmaking is shared with several levels of government or devolved administrations.

The relationship between agricultural AMU and AMR is not straightforward; variations across agri-systems provide an opportunity for comparative study to disentangle this relationship. Priorities for bilateral work in this area include gaining deeper understanding of the drivers of AMU, and how AMU (and changes in AMU) relates to AMR (and role of minimum inhibitory concentrations in controlling AMR); characterizing UK and Canada agri-systems; developing more Point-of-Care (POC) diagnostics; innovating safe, well-evidenced and low-cost alternatives to AMU to maintain animal health and welfare; sustaining investment and partnerships to strengthen the next generation of research talent.

THEME 2 Highlights. Canada and the UK have unique research and innovation strengths to leverage in addressing AMR transmission between reservoirs of AMR. These include: i. national AMR surveillance programs (Canada's integrated national surveillance program, UK's multiagency surveillance program); ii. AMR research funding e.g. Canada's Genomics R&D Initiative (GRDI) and

UK's PATH-SAFE initiative to pilot a national farm-to-fork surveillance network using the latest genomic technologies; and iii. the fact that both are moving towards a 'One Health' approach to tackling AMR.

There are considerable knowledge gaps concerning the AMR burden in animals and interactions with the environment. Not only do we need a better understanding of the factors, both on farm and in the wider environment, that contribute to the selection and transmission of AMR, but we must be able to gauge the health of ecosystems in (near) real-time. Priorities for bilateral work in this area include generating accurate and timely estimates of the magnitude and trends in AMR burden in animals and the environment; widening sampling beyond specific pathogens to improve knowledge of AMR ecology (sharing genomic and phenotypic data could help); understanding the role of animal vectors and gut microbiome in AMR transmission; evaluating the utility of bioindicators, waste streams, and other indicators to gauge the health of ecosystems; and validating existing food safety practices with respect to protection against AMR.

THEME 3 Highlights. Unique research and innovation strengths in Canada and UK in genomics to improve AMR surveillance include the UK's successful effort in rapidly firing up decentralized sequencing across the UK during the COVID-19 pandemic. Valuable data tools have been developed in both the UK and Canada, plus both countries have large AMR surveillance datasets and historical collections of pathogenic microbes, which afford significant opportunities for data analysis and discovery. Capitalizing on the infrastructure developed during the COVID-19 pandemic to track the emergence and spread of virus variants (with clear applications in AMR surveillance) seems imperative.

Future AMR surveillance and mitigation efforts will need to incorporate gene level understanding of resistance and transmission, including the role of associated mobile genetic elements (MGEs) such as plasmids and prophages. This would help fill in gaps in our knowledge surrounding AMR emergence and directionality of transmission. Additional priorities for bilateral work in this area include development of artificial intelligence (AI) and machine learning (ML) tools to predict phenotypic AMR from genomic data; designing surveillance systems and analysis pipelines around resistomes and metagenomics data; establishing exposure assessments and risk levels that trigger mandating standards; addressing known bottlenecks in tackling AMR and, as much as possible, cooperating on the standardisation of data sampling and analysis pipelines.

The workshop identified shared research priorities and areas where the two countries have research strengths that could provide the basis for future UK-Canada collaboration. Next is the task of identifying joint thematic priorities of interest to both parties in anticipation of collaborative project planning and associated funding calls.

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ACKNOWLEDGMENTS

The **UK-Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment** was made possible thanks to the efforts and support of its many participants and their respective organizations.

Funding support is gratefully acknowledged from these sponsors: Genome Canada, Genome Alberta, the United Kingdom Research and Innovation (UKRI), UKRI Natural Environment Research Council (NERC), UKRI Medical Research Council (MRC), UKRI Biotechnology and Biological Sciences Research Council (BBSRC), AMR One Health Consortium and One Health at UCalgary.

Special thanks are extended to workshop organizing committee members: Michele Anholt (Manager, One Health at UCalgary), David Bailey (CEO, Genome Alberta), Herman Barkema (Director, One Health at UCalgary), Andrea Kormylo (Administrative Coordinator, One Health at UCalgary), Evangelia Kougioumoutzi (Head of European and Global Partnerships, BBSRC-UKRI), Samantha Larose (Manager, AMR - One Health Consortium) and Emily Wheater (Portfolio Manager - International, BBSRC-UKRI).

This final report was prepared by Susan Joyal-Coleman (Canada) and Emily Wheater (UK), with editorial assistance from the organizing committee.

Territorial Acknowledgement

The workshop was hosted and broadcast from Calgary, which is located on the traditional territories of the people of Treaty 7 region in Southern Alberta (Canada), which includes the Blackfoot Confederacy comprising the Siksika, the Piikani, and Kainai First Nations as well as the Tsuut'ina First Nation, and the Stoney Nakoda, including the Chiniki, Bearspaw, and Wesley First Nations. The City of Calgary is also home to the Métis Nation of Alberta, Region Three. The University of Calgary is situated on land adjacent to where the Bow River meets the Elbow River, and the traditional Blackfoot name of this place is Moh'kins'tsis, which we now call the City of Calgary.

I. INTRODUCTION

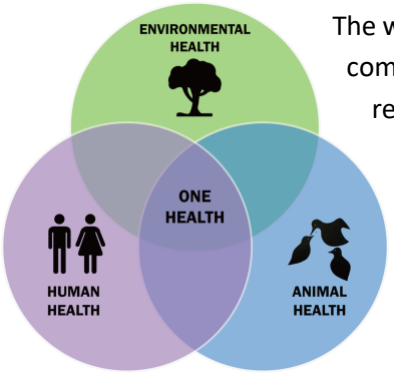
Globally, Antimicrobial Resistance (AMR) kills >700K people annually and, by 2050, that number is predicted to rise to >10M deaths annually at a cost of US$100T [1]. Early news in an upcoming report (autumn 2021) by the Institute for Health Metrics and Evaluation (IHME) on its Global Research on Antimicrobial Resistance (GRAM) Project [2] suggests the toll is, and will be, much higher. Despite this, it is still possible to change the trajectory and significantly lessen the threat AMR poses to the world and its inhabitants. As Dame Sally Davies, UK's Special Envoy on AMR, counselled, "it is the job of scientists to help leaders and decision makers untangle complex global challenges (like AMR)".

Antimicrobials – including antibiotics, antivirals, antifungals and antiparasitics – are medicines used to prevent and treat infections in humans, animals, and plants.

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective and infections become increasingly difficult or impossible to treat.
WHO, 2020

In late July 2021, experts on Antimicrobial Resistance (AMR) from academia, government, and industry were invited to participate in a **UK-Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment** (September 23, 2021) co-hosted by United Kingdom Research and Innovation (UKRI), Genome Alberta, One Health at UCalgary and the AMR – One Health Consortium. Workshop presentations and breakout sessions were organized into three themes important to both countries' agricultural and environmental sustainability and profitability:

1. Antimicrobial Use (AMU) and Antimicrobial Resistance (AMR) *within reservoirs of AMR*: farm animals, on farm, and wider environments
2. Transmission of AMR *between reservoirs of AMR*: in agriculture, the environment, and to humans
3. Use of genomics to improve AMR surveillance



The workshop agenda is in appendix a. Confirmed delegates were asked to complete a survey (appendix b) electronically prior to the meeting. Their responses were collated, and results used to craft questions for discussion in the breakout sessions. A synthesis of survey responses, organized by theme, has also been included in appendix b. Ultimately, the objective of this workshop was to better understand UK and Canada's research strengths and gaps regarding AMR and use this knowledge to help identify future opportunities for bilateral collaborations.

[1] The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, December 2014
[2] http://www.healthdata.org/gram

II. UK-Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment

AMR leaders from academia (45%), industry (7%) and government (48%) participated virtually in the workshop. A total of 71 individuals (appendix c), 35 from the UK (26 delegates, 4 presenters, 4 facilitators, 1 coordinator) and 36 from Canada (26 delegates, 4 presenters, 4 facilitators, 2 coordinators), attended the four-hour event. Brief biographies of presenters are in appendix d. The presentations were video recorded, and a link is included in appendix e along with summary notes for each presentation (links to information sources referenced are also provided). Additionally, summary notes for the breakout sessions, distinguished by theme, are in appendix f. Facts and insights gleaned from those summary notes appear throughout the body of this report and readers are urged to consult the appropriate appendices to ascertain authorship.

THEMES

1) Antimicrobial Use (AMU) and Antimicrobial Resistance (AMR) *within reservoirs of AMR*: farm animals, on farm, and wider environments

Globally, >80% of antibiotics are used in farming, rather than human patients. Estimates point to a 67% increase in global consumption of antibiotics by 2030, with 70% of the world's largest protein companies deemed "high risk" for antibiotic stewardship. Antibiotics aren't the only antimicrobials contributing to AMR; there are increasing concerns about the use of antifungals and antiparasitics in agriculture and aquaculture. AMR is not a local problem, it is a global problem that affects inhabitants the world over, in high income and low- and middle-income countries (LMICs). Our planet is already polluted with antimicrobials and AMR microorganisms that threaten the health of all ecosystems. AMU and AMR stewardship is a shared responsibility. While hopeful efforts are underway globally, experts agree on the need for a fully integrated One Health approach to AMR. Key will be cleaning up and transforming our food systems to be more resilient, sustainable, and equitable. Better AMR surveillance in agriculture (animal, fish, crop) and the environment, plus the innovation of safe and effective alternatives to antimicrobials to help curb their misuse and overuse, are paramount.

1.1 Unique Features of UK and Canada Agri-Systems, Natural Environments, and Cultures that may foster AMU and AMR *Within Reservoirs of AMR*

Differences in farm number (UK>Canada), average farm size (Canada>UK), cropland (Canada>UK) and cropping systems, livestock inventories (cattle, pigs, poultry: Canada>UK; sheep: UK>Canada) and livestock management systems (single species vs. mixed, intensive vs. extensive, etc.), were noted. Publications and infographics, available from government websites[3], help to characterize agri-systems in each country. For both, the categorization of antimicrobials has been key in tackling AMU and AMR.

[3] UK: Agriculture in the United Kingdom, 2020
Canada: 150 Years of Canadian Agriculture, A portrait of Canadian Farms

The use of antibiotics as growth promoters in livestock was banned (2006 in UK; 2018 in Canada) and livestock farmers now require a veterinary prescription to treat their animals with antibiotics. It's worth noting that reduced AMU, witnessed in both countries, has been largely voluntary (by industries themselves). Still, regulations concerning AMU differ between the UK and Canada. In both countries, the responsibility for lawmaking is shared. In Canada, it is shared by one federal, ten provincial, and three territorial governments. In the UK, it is shared with the devolved administrations of Scotland, Wales, and Northern Ireland. This often complicates the regulatory landscape.

1.2 Research Needs, Gaps, and Opportunities for Implementing Alternatives to Antimicrobials and Reducing Selection and Transmission ***Within Reservoirs of AMR***

- There is a need to better understand the drivers of AMU in agri-systems.
- The relationship between AMU and AMR isn't straightforward and more research is required to address this knowledge gap.
- The impact of changes in AMU on AMR, and in different settings, is not well understood (e.g., accounting for animal welfare, societal impacts).
- There is demand from farmers and veterinary practitioners for more point-of-care (POC) diagnostics, but there are barriers to innovation of these tools.
- We need more safe, low cost, and effective alternatives to antimicrobials, with strong evidence supporting their use and accounting for animal welfare and quality of produce.
- We still don't know the full extent of AMU in agriculture (species-specific licenses apply).
- More evidence is needed to assess impacts of current regulatory environment on AMR initiatives.
- It is vital that we support younger generations and researchers tackling AMU and AMR, with an emphasis on interdisciplinary training.

1.3 Bilateral Partnership Opportunities between Canada and the UK

For all opportunities listed, pre-study consultations between UK and Canada experts regarding data sampling | standards | sharing, as well as knowledge and technology transfer, are encouraged:

- Determine AMU drivers and better characterize AMU-AMR relationship in agri-systems (livestock, crops, livestock-crop, aquaculture) and the environment in both countries using genomics.
- Undertake comprehensive characterization of UK and Canada agri-systems (include aquaculture), natural environments, cultures, and regulatory environment, with respect to AMU and AMR.
- Characterize ecology and changes in bacterial populations, plus impacts on animal welfare and society, resulting from AMU (antibiotics, antifungals, antiparasitics) changes in different settings and ascertain role minimum inhibitory concentrations (MICs: 'gold standard' for determining susceptibility of organisms to antimicrobials) in controlling AMR.
- Develop POC diagnostics to help ensure 'right drug for right bug' is used (and AMU is reduced).
- Innovate safe, low cost, effective, and easy to implement alternatives to antimicrobials.
- Compile a handbook listing all antimicrobials licensed for use in UK and Canada, with species noted and make use of available prescription records.
- Identify bottlenecks in UK and Canada regulatory environments, coordinate regulatory & policy decisions re: AMU.

- Sustain investment and partnerships to strengthen the next generation of research talent and support Early Career Researchers (ECRs) (e.g., CRCC-UKRI collaboration[4]), with strong emphasis on interdisciplinary AMR training (also, consider UK-Canada postdoctoral exchange programs).

2) Transmission of AMR *between reservoirs of AMR*: in agriculture, the environment, and to humans

Antibiotic resistance in pathogenic bacteria is not a modern phenomenon – there is evidence of resistance mechanisms from over 2 billion years ago. In a 2011 study, researchers reported a huge variety of Antimicrobial Resistance genes (ARGs) in 30,000-year-old Beringian permafrost. Today, we know the environment is widely contaminated with antibiotic resistant bacteria associated with human activity, and that resistance is transferred through fecal contamination; in situ selection for AMR has also been confirmed. Clearly, we must consider agricultural and natural environments when addressing the problem of AMR.

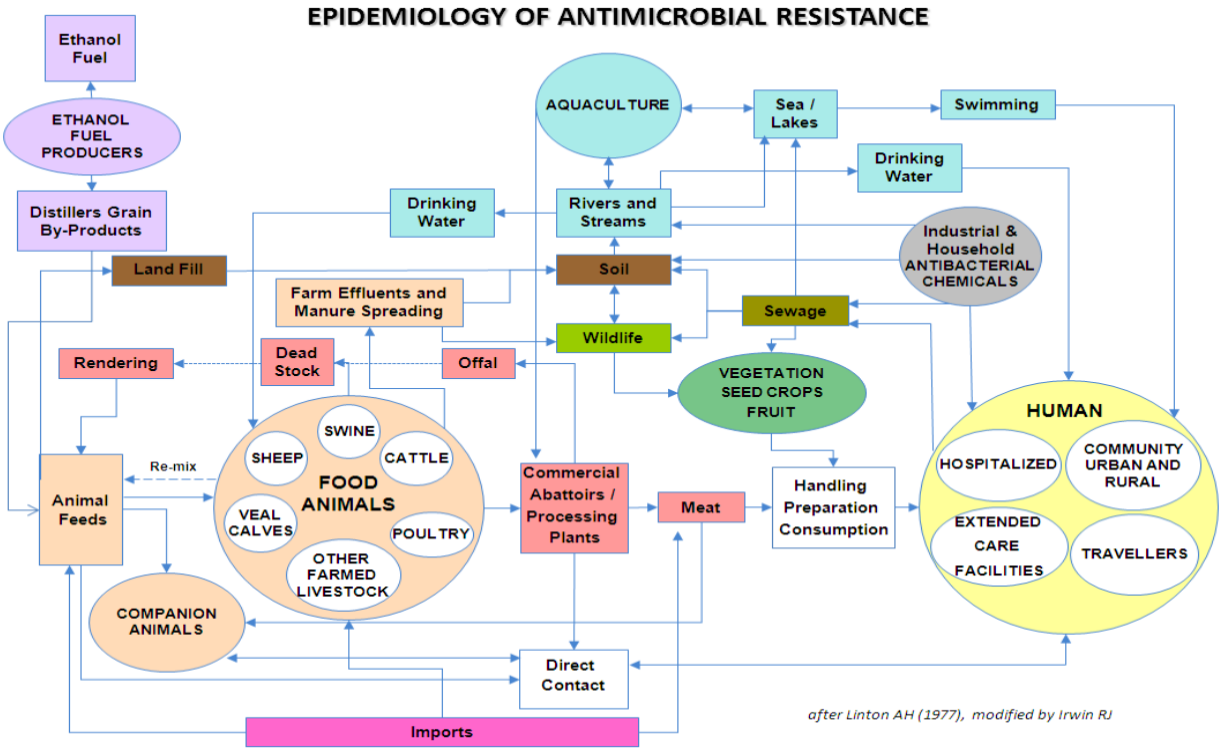


Figure 1. The Epidemiology of Antimicrobial Resistance[5] ("The Confusogram")

The epidemiology of AMR was first illustrated in 1977 and updated in 2014 (Figure 1). Despite advances, knowledge gaps about AMR selection and transmission (including directionality) persist. For that reason, workshop participants sometimes referred to Figure 1 as, "The Confusogram". Researchers have a better understanding today of AMR in distinct reservoirs but more information, especially in agriculture (animals, fish, crops) and the environment (built and natural), is required.

[4] Mobilizing Canadian Research Progress Report (2019-20)

[5] https://www.canada.ca/en/public-health/services/surveillance/canadian-integrated-program-antimicrobial-resistance-surveillance-cipars/background.html

Additional research on AMR transmission at human | animal | environment interfaces is also needed. There are knowledge gaps regarding the impact of interspecies interactions and the built environment on AMR. Understanding the ecology of AMR is vital, and so environmental sampling and microbiome sampling (ideally at resistome level using metagenomics) are preferred over focused investigations of specific pathogens as research efforts continue.

2.1 Unique Research and Innovation Strengths in Canada and UK to Address AMR Transmission ***Between Reservoirs of AMR***

In Canada, the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) monitors AMU and AMR in selected bacteria from humans (Public Health Agency of Canada (PHAC)'s Canadian Antimicrobial Resistance Surveillance System (CARSS)), animals (farm, abattoir, veterinary practices), and animal-derived food sources (retail) across Canada. Additionally, the Genomics R&D Initiative (GRDI), which maintains core genomics capacity (annual funding ~$20M), has a strategic research program for AMR (2016-present) with this overarching goal: to identify targets for action through mapping the development and transit of AMR through healthcare, animals, plants, and the environment to preserve the effectiveness of the antimicrobials that Canadians rely on every day.

In the UK, AMU in agriculture and AMR in the food chain are monitored by the Veterinary Medicines Directorate (VMD), the Animal and Plant Health Agency (APHA), and the Food Standards Agency (FSA). Recently, the cross-departmental project team behind UK's Pathogen Surveillance in Agriculture, Food, and the Environment (PATH-SAFE), was awarded £19.2M to develop a pilot national farm-to-fork surveillance network using the latest genomic technologies. Both Canada and the UK are moving towards a One Health model to tackle AMR. The UK has expertise in animal models of transmission and the emergence of AMR. Canada's AMR Network recently published a report titled, "Strengthening Governance of the Antimicrobial Resistance Response Across One Health in Canada"[6].

2.2 Research Needs, Gaps, and Opportunities for Implementing Alternatives to Antimicrobials and Reducing Selection and Transmission ***Between Reservoirs of AMR***

- Better quantify AMR burden (magnitude, trends) in animals and the environment; currently much surveillance activity relies on qualitative assessment (e.g., present/absent).
- Identify factors that contribute to selection and transmission of AMR in livestock agriculture, plant-based systems, and aquaculture.
- Gain a broader understanding of AMR ecology and prediction of AMR hotspots; artificial intelligence (AI) and machine learning (ML) tools may help.
- There is a knowledge gap around how contaminated vectors (e.g., seafood, migratory birds, food imports/exports) contribute to the spread of AMR globally.
- The role of the gut microbiome (believed to be a reservoir for ARGs) in AMR transmission is not well understood.

[6] Strengthening Governance of the Antimicrobial Resistance Response Across One Health in Canada, June 2021

- We need to gauge the health of ecosystems better; evidence-based bioindicators and consideration of waste streams will be crucial.
- The efficacy of existing food safety practices in protecting consumers against AMR should be evaluated.

2.3 Bilateral Partnership Opportunities between Canada and the UK

For all opportunities listed, pre-study consultations between UK and Canada experts regarding data sampling | standards | sharing, as well as knowledge and technology transfer, are encouraged:

- Generate accurate and timely estimates of the magnitude and trends in AMR burden in animals and the environment (like the upcoming IHME GRAM[7] report); Transatlantic Task Force on Antimicrobial Resistance (TATFAR[8]) provides a framework for collaboration.
- Undertake One Health studies to ascertain associations between human | animal | environment and bacterial populations (rely on microbiome sampling and environmental sampling (and not just a limited number of specific pathogens) to truly understand ecology of AMR). Parallel longitudinal studies that incorporate stratified sampling across both countries would be especially valuable.
- Share genomic and phenotype data (standardisation of data, data analysis methods and nomenclature would be needed) to better understand AMR ecology.
- Study the role of migratory contaminated animal vectors in the spread of AMR globally.
- Investigate the role of gut microbiome in AMR transmission (technology to image gut microbiome and observe effect of probiotics would be helpful too).
- Evaluate utility of bioindicators and waste streams (distinguish between fecal and non-fecal waste) to gauge the health of ecosystems.
- Validate existing food safety practices with respect to protection against AMR; compare domestic and imported fruits and vegetables (antibiotics are used in orchards in Canada but not in the UK).

3) Use of genomics to improve AMR surveillance

Resistance is complex and it's important to consider the microbial world in all its scales: the sheer number of microbes (best guess) is 5×10^{30}, its high speed of reproducing, and the many ways of exchanging DNA[9]. To make true progress in combatting AMR, the transmission of resistance must be understood at the gene level. Genomics has already helped researchers identify ARGs and mobile genetic elements (MGEs), such as plasmids and prophages, involved in the transmission of resistance across the One Health continuum, but more knowledge is needed still. For example: it's possible to identify MGEs but researchers aren't clear on what makes them tick or move around; it's possible to map transfers of resistance but large divergences and differences remain unexplained; it's possible to

[7] http://www.healthdata.org/gram

[8] TATFAR (est. 2009) addresses the urgent threat of antibiotic resistance. TATFAR's technical experts from Canada, the EU, Norway, and the USA collaborate and share best practices to strengthen domestic and global efforts.

[9] (1) transformation: bacterium takes up a piece of DNA floating in its environment, (2) transduction: DNA accidentally moved from one bacterium to another by a virus, (3) conjugation: DNA is transferred between bacteria through a tube between cells, (4) transposable element: segments of DNA that can change position within a genome.

look for signatures of risk in microbial genomes to predict AMR, but when predictive models fail researchers have yet to figure out which key pieces of information are still missing. Answers to these questions and more, plus a better understanding of how everything ties together, are certain to bolster future AMR surveillance efforts.

Genomic epidemiology aims to distinguish cases of a pathogen (related vs. unrelated) and identify risk using genomics. The process (collect samples, sequence genomes, compare genome sequences and determine relatedness, map information against clusters of genomically similar sequences, assess risk) is scalable and has already proven to be an invaluable part of AMR surveillance programs. That said, focusing on specific pathogens only affords a tiny snapshot of what's going on in the whole resistome and has been characterized as a reactive approach. A more proactive approach would be to expand surveillance to include microbiomes (may help detect AMR seeding events) and look at the resistome level (especially at the interface of animal | environment | human) using metagenomics.

3.1 Unique Research and Innovation Strengths in Canada and UK in Genomics to Improve AMR Surveillance

The COVID-19 Genomics UK Consortium (COG-UK) was demonstrably successful in rapidly firing up decentralized sequencing across the UK, along with standardised and centralised data processing and analysis, to better understand the SARS-COV-2 virus. That expertise should be exploited when organizing efforts around AMR. Valuable data tools were developed recently in the UK (Epicollect5, Microreact, Pathogenwatch, Data-flo) and Canada (IslandCompare), and consideration should be given to pivoting those tools to help identify and track lineages and variants of AMR.

Both Canada and the UK have historical collections of pathogenic microbes (e.g., Murray Collection, the National Collection of Pathogenic Fungi, CABI) predating the discovery and widespread use of antimicrobials. Exploring these under-utilized resources could aid in the understanding of horizontal gene transfer and the phenotypic emergence of AMR. Additionally, both countries have large AMR surveillance datasets that would afford plenty of data analysis opportunities.

3.2 Research Needs, Gaps, and Opportunities in Genomics for Implementing Alternatives to Antimicrobials and Reducing Selection and Transmission of AMR

- A gene level understanding of resistance and transmission is critical.
- More accurate prediction of phenotypic AMR from genotypic data is needed.
- Proactive AMR surveillance programmes (One Health approach) that focus more on resistomes (and less on specific pathogens) will aid in identifying the emergence of AMR and tracking transmission.
- Establishing exposure assessments and risk levels that trigger mandating standards is important.
- We must address known bottlenecks (e.g., data and data tools, data analysis (especially for volumes of data already collected), genomics-epidemiology link, rapid interpretations, political and supply chain issues) when tackling AMR.
- Standardisation of data collected, sampling methods, and analysis pipelines will help ensure more meaningful comparisons of UK-Canada projects.

3.3 Bilateral Partnership Opportunities between Canada and the UK

For all opportunities listed, pre-study consultations between UK and Canada experts regarding data sampling | standards | sharing, as well as knowledge and technology transfer, are encouraged:

- Acquire gene level understanding of ARGs transmission and associated MGEs between microorganisms. Consider construction and analysis of "meta" AMR databases using existing databases (e.g., CARD, PhA4ges,).
- Develop AI and ML tools to better predict phenotypic AMR from genomic data.
- Design an AMR surveillance program with AI/ML capabilities to aid in genotype-to-phenotype prediction that focuses on resistomes, especially at animal | environment | human interfaces, using metagenomics. Note: infrastructure established in UK for monitoring COVID-19 variants could be adapted to the challenge of AMR.
- Define a hazard component for AMR risk assessments (part of genomics epidemiology process).
- As a first step in addressing known bottlenecks in tackling AMR, conduct a landscape scan and develop a strategic plan on how best to address bottlenecks.
- For collaborative UK-Canada projects, thorough descriptions of sampling methods (ideally, standardized before data was collected) would be very helpful. Similarly, cooperation on the standardisation of analysis pipelines (consider using Cloud Infrastructure for Big Data Microbial Bioinformatics (CLIMB)) would be advantageous.

III. CLOSING REMARKS

The **UK-Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment**, which included a pre-workshop survey, several presentations and breakout room discussions, satisfied the objective of better understanding UK and Canada's research strengths and gaps regarding AMR. This provides a foundation for identifying future opportunities for bilateral collaborations. All that was written, presented, and discussed in the workshop has been documented in this final report. We wish to thank all presenters, attendees, facilitators and organizers for their help in making this workshop possible. In concluding her presentation, Dame Sally Davies remarked that "all of us have a responsibility to turn numbers and ideas into meaningful and sustainable action". This is apt as we contemplate and collaborate on the next best steps.

IV. NEXT STEPS

This report will be distributed to all attendees of the workshop. It will provide a foundation for future internal discussions between agencies to identify thematic priorities, and UK-Canada decisions around where/whether to proceed on bilateral collaborations. Based on discussions summarised in this report, thematic priorities will be identified and further consultation with experts from each country will continue if necessary. In readiness for joint funding and project planning in these areas, there will be continued engagement between the UKRI and Canadian agencies.

V. APPENDICES

a) Workshop Agenda

UK – Canada One Health Workshop on Antimicrobial Resistance in Agriculture and the Environment

Thursday, September 23, 2021

AGENDA

8:00 MDT 15:00 BST	Welcome *David Bailey, Genome Alberta*
8:05 MDT 15:05 BST	Introduction and overview of the day *Kathy McCoy, University of Calgary* *Kristen Reyher, University of Bristol*
8:10 MDT 15:10 BST	Keynote presentation *Dame Sally Davies, UK Special Envoy on Antimicrobial Resistance*
8:30 MDT 15:30 BST	Presentations related to: Antimicrobial use (AMU) and AMR in farm animals and in farm and wider environments *Tim McAllister, Agriculture and Agri-Food Canada* *Kristen Reyher, University of Bristol*
9:00 MDT 16:00 BST	Presentations related to: Transmission of AMR in agriculture, the environment, and to humans *Will Gaze, University of Exeter* *Ed Topp, Agriculture and Agri-Food Canada*
9:30 MDT 16:30 BST	Presentations related to: Use of genomics to improve AMR surveillance *David Aanensen, University of Oxford* *Rob Beiko, Dalhousie University*
10:00 MDT 17:00 BST	Break
10:10 MDT 17:10 BST	Introduction to breakout sessions
10:20 MDT 17:20 BST	Breakout rooms *Each addressing the findings from the main questions on the Qualtrics survey, keeping in mind the 3 pillars and the priorities of each delegates respective organization/country.*
11:00 MDT 18:00 BST	Report back and group discussions on each question
11:45 MDT 18:45 BST	Discussion on next steps
12:00 MDT 19:00 BST	Adjournment

Zoom link: https://ucalgary.zoom.us/j/93872178435
Meeting ID: 938 7217 8435
Passcode: 034648

b) Pre-Workshop Survey Questions and UK-Canada Synthesis of Responses

1. What are the unique strengths of research, innovation, facilities, and infrastructure for AMR research in your country?
2. Describe how your country's genomic capabilities can improve AMR surveillance systems; what are the knowledge gaps?
3. Describe the features of your country's agri-systems, cultures and natural environments which would benefit from bi-lateral collaboration, to understand their impact on AMR?
4. Describe your country's AMR and AMU surveillance methodologies and scope with consideration of AMR reservoirs and transmission pathways.
5. What are the research needs and opportunities for implementing alternatives to antimicrobials, in order to reduce selection and transmission of AMR in humans, animals, plants and the natural environment (e.g. standards for antimicrobial discharge into rivers and farm management practices)?
6. Vaccine platforms are the backbone or delivery vehicle that a new gene or protein of interest is inserted into. They consist of classical vaccine platforms (such as inactivated viruses), and next generation vaccine platforms (such as nucleic acid-based vaccines, consisting of DNA or mRNA). Identify how existing vaccine platforms can help combat AMR in animals.
7. What are the key areas for potential partnerships in AMR research between Canada and the UK? Please consider AMR research priorities and needs.
8. What is the potential for agreed upon data standards and data sharing between Canada and the UK?
9. What key areas can be covered by existing partnerships or national interventions (e.g. around stewardship, practice standards in infection prevention etc.) and which areas still need to be addressed?
10. Where are the opportunities for cross-disciplinary collaborative research between Canada and the UK examining the cultural, social, behavioural, and economic drivers of AMR development in agricultural and environmental contexts?
11. How can research outcomes from the above priorities be best communicated to influence Government policy and regulations, in the UK and Canada?

UK-Canada Synthesis

THEME 1: Antimicrobial Use (AMU) and Antimicrobial Resistance (AMR) *within reservoirs of AMR*: farm animals, on farm, and wider environments

- UK and Canada represent different environments, with the UK having proportionally more free-range farming, smaller farms, and reducing AMU. The two systems are also subject to different regulations. Comparative analyses, capitalising on these differences and similarities, would identify variables that impact emergence, spread and transmission of AMR.
- Need to understand drivers of AMU in agriculture, be they social, economic, behavioural, or political. This is a key opportunity for interdisciplinary research.

- Building an evidence base for preventative measures such as improved management practices (for example, waste management and antimicrobial discharge from agriculture into the environment) and vaccination programmes to reduce infection and disease burden.
- Alternatives to antimicrobials for managing infections (such as phage therapy, plasmid curing) and as growth promoters (probiotics). Need to understand the balance of cost-benefit in terms of efficacy and environmental impact, and economic viability.
- Need to better understand the impact of AMU in agri/aquaculture on zoonotic transmission of AMR to humans, and into the environment. Canada identified UK as having a particular strength in aquaculture.

THEME 2: Transmission of AMR *between reservoirs of AMR*: in agriculture, the environment, and to humans

- Both countries described surveillance and technological capability as strong. However, both also described environmental surveillance as lacking/sporadic. This is a barrier to understanding in AMR transmission pathway and the impact of AMU in human/animals on the environment.
- Variety of different environment types need to be investigated, such as built up, open rural/urban.
- In environmental surveillance there is a need to determine surveillance end points, such as relevant and evidence-based thresholds of antimicrobials in the environment (below minimal selective threshold).
- Although both countries identified strong links between industry/academia/government in AMR, surveillance can end up siloed within domains, such as hospitals, food processing, agriculture, ad with differences between regional or devolved governments. Integration between surveillance systems, standardisation of data collection/metadata is needed to ease analysis across industries and to understand directionality of transmission pathways, such as the contribution of animal AMR reservoirs to human.

THEME 3: Use of genomics to improve AMR surveillance

- Both UK and Canada identified genomics and associated facilities as strengths. Canada particularly highlighted ML and AI and computational capacity. UK highlighted sequencing capability as a strength.
- Both countries identified 'genotype to phenotype' limitation of genomic approaches; there is a need to understand gene expression changes that give rise to AMR, and that the presence of an AMR gene does not always correspond to phenotypic AMR. Canada has an opportunity here due to phenotypic data on a large proportion of dairy cattle thanks to the Milk Recording Organisation.
- Incorporating genomics into standard surveillance practices for rapid identification of emerging AMR and real time alerts systems. Metagenomic approaches would uncover ecology of Antimicrobial Resistance organisms, and the broader microbiome. Surveillance has previously focused on 'priority' pathogens (*Salmonella, Campylobacter, E. coli*), and expanding this out to other microbes including viruses, fungi would be informative. UK identified metagenomics as a potential area of skills deficit.
- Genomics informed diagnostics, in both animal and human settings, would enable better specificity of AMU in response to infection.

c) List of Workshop Attendees

NAME	COUNTRY	ORGANIZATION
PRESENTERS		
David **Aanensen**	UK	University of Oxford
Robert **Beiko**	Canada	Dalhousie University
Dame Sally **Davies**	UK	UK Government
Will **Gaze**	UK	University of Exeter
Tim **McAllister**	Canada	Agriculture and Agri-Food Canada (AAFC)
Kathy **McCoy**	Canada	University of Calgary
Kristen **Reyher**	UK	University of Bristol
Ed Topp	Canada	Agriculture and Agri-Food Canada (AAFC)
DELEGATES		
Ian **Alexander**	Canada	Canadian Food Inspection Agency (CFIA)
Muna **Anjum**	UK	Animal and Plant Health Agency (APHA)
Matthew **Avison**	UK	University of Bristol
Herman **Barkema**	Canada	University of Calgary
Patrick **Bastedo**	Canada	Public Health Agency of Canada (PHAC)
Catherine **Carrillo**	Canada	Canadian Food Inspection Agency (CFIA)
Carolee **Carson**	Canada	Public Health Agency of Canada (PHAC)
Ivana **Cecic**	Canada	Genome Canada
Clare **Chandler**	UK	London School of Hygiene and Tropical Medicine (LSHTM)
John **Conly**	Canada	Alberta Health Services (AHS), University of Calgary
Tania **Dottorini**	UK	University of Nottingham
Edward **Feil**	UK	University of Bath
Mathew **Gilmour**	UK	Quadram Institute
Alwyn **Hart**	UK	Environment Agency
Fiona **Henriquez-Mui**	UK	University of the West of Scotland
Jay **Hinton**	UK	University of Liverpool
Jon **Hobman**	UK	University of Nottingham
Mary-Jane **Ireland**	Canada	Canadian Food Inspection Agency (CFIA)
Moses **Iziomon**	Canada	Agriculture and Agri-Food Canada (AAFC)
David **Kelton**	Canada	University of Guelph
Evangelia Kougioumoutzi	UK	UKRI Biotechnology and Biological Sciences Research Council (BBSRC)
Roberto **La Ragione**	UK	University of Surrey
Kathleen **Long**	Canada	Maple Leaf Foods
Catalina **Lopez-Correa**	Canada	Genome Canada
Jacob **Malone**	UK	John Innes Centre
Alison **Mather**	UK	Quadram Institute

Tim **Mauchline**	UK	Rothamsted Research
Kimberley **Meadows**	Canada	Canadian Food Inspection Agency (CFIA)
Manisha **Mehrotra**	Canada	Health Canada
Dominic **Moran**	UK	University of Edinburgh
Jennifer **Morgan**	UK	UK Research and Innovation (UKRI)
Andrew **Morris**	Canada	Mt. Sinai Hospital
Mike **Mulvey**	Canada	University of Manitoba
Simon **Otto**	Canada	University of Alberta
Chris **Pinto**	UK	London School of Hygiene & Tropical Medicine (LSHTM)
Sonny **Rathod**	UK	UK Research and Innovation (UKRI)
Richard **Reid-Smith**	Canada	Public Health Agency of Canada (PHAC)
Mark **Reist**	Canada	Health Canada
Lorna **Richardson**	UK	EMBL - European Bioinformatics Institute (EBI)
Jennifer **Ritchie**	UK	University of Surrey
Matthew **Ryan**	UK	Centre for Agriculture and Bioscience International (CABI)
Javier **Sanchez**	Canada	University of Prince Edward Island
Karin **Schmid**	Canada	Alberta Beef
Andrew **Singer**	UK	UK Centre for Ecology & Hydrology
Jonathan **Statham**	UK	RAFT Solutions – Industry
Kevin **Tiessen**	Canada	International Development Research Centre (IDRC)
Rob **Tremblay**	Canada	Boehringer-Ingleheim
Susan **Rogers van Katwyk**	Canada	WHO Collaborating Centre on Global Governance of AMR
Willem **van Schaik**	UK	University of Birmingham
Scott **Weese**	Canada	Ontario Veterinary College, University of Guelph
Gerry **Wright**	Canada	McMaster University
Xiangming **Xu**	UK	NIAB East Mailing Research (EMR)
FACILITATORS		
Michele **Anholt**	Canada	One Health at University of Calgary
David **Bailey**	Canada	Genome Alberta
Carolyn **Johnson**	UK	UKRI Medical Research Council (MRC)
Samantha **Larose**	Canada	One Health at University of Calgary
Colin **Miles**	UK	Translational and Clinical Research Institute (TCRI)
Liz **Rowse**	Canada	Natural Environment Research Council (NERC)
Stephen **Webb**	UK	UKRI Biotechnology and Biological Sciences Research Council (BBSRC)
Emily **Wheater**	UK	UKRI Biotechnology and Biological Sciences Research Council (BBSRC)
COORDINATORS		
Susan **Joyal-Coleman**	Canada	Genome Alberta (Contract)
Andrea **Kormylo**	Canada	One Health at University of Calgary
Elizabeth **Wellington**	UK	University of Warwick

d) Workshop Presenter Biographies

Aanensen, David Ph.D. Bioinformatics, M.Sc. Neuroscience

- David Aanensen is the Director of the Centre for Genomic Pathogen Surveillance (CGPS) which is based at The Wellcome Sanger Institute brings together expertise in data modeling, software development, epidemiology, bioinformatics and machine learning, genomic technology, Good Financial Grant Practice (GFGP), training and capacity building. David is also a Senior Group Leader in Genomic Surveillance at the Big Data Institute, University of Oxford.

Beiko, Rob Ph.D. Biology Bioinformatics, B.Sc. (Honours) Biology Genetics

- Rob Beiko is Professor and Associate Dean of Research in the Faculty of Computer Science at Dalhousie University. Research topics: Bioinformatics, Comparative genomics and phylogenetics, Machine learning, Visualization of biological data, Human microbiome.

Davies, (Dame) Sally GCB, DBE, FRS, FMedSci

- Dame Sally Davies was installed as the 40th Master of Trinity College on 8 October 2019. She joined the College after a distinguished career as a clinical academic and public servant. Dame Sally graduated from Manchester Medical School in 1972 and became a Consultant Haematologist specialising in sickle cell disease. In 1997 she was appointed as Honorary Professor of Haemoglobinopathies at Imperial College. Dame Sally was the Chief Scientific Adviser to the Department of Health from 2004-2016. In 2006 she founded the National Institute of Health Research (NIHR) and was the Inaugural Director. In 2013 she established and became a Non-Executive Director of Genomics England Ltd (GEL) which sequenced 100,000 whole genomes of NHS patients. Dame Sally was the Chief Medical Officer for England and Senior Medical Advisor to the UK Government from 2011-2019. She authorised 11 independent annual reports and 3 special reports: Medical Cannabis, Screen Times for Children and Obesity in Childhood. She has become a leading figure in global health including serving as a member of the World Health Organisation (WHO) Executive Board 2014-2016 and as co-convener of the United Nations Inter-Agency Co-ordination Group (IACG) on Antimicrobial Resistance (AMR) reporting in 2019. She has championed the need to address AMR across all sections: human and animal health, agriculture and environment within the UN family and globally. In 2019 Dame Sally was appointed as the UK Government's Special Envoy for Global AMR. Dame Sally received her DBE in 2009. She was elected Fellow of the Royal Society in 2014 and a member of the National Academy of Medicine, USA in 2015. She has been awarded more than 30 honorary doctorate degrees.

Gaze, Will Ph.D. Aquatic ecology, B.Sc. Marine Biology

- Professor Will Gaze has over 15 years' experience of Antimicrobial Resistance research in farmed and natural environments, including major elements of environmental sampling and wide-ranging analytical methodologies. His research group consists of over 20 researchers funded by over £4 million in current and recent Antimicrobial Resistance (AMR) grants. Current activity within Prof Gaze's group covers fundamental issues of AMR evolution in the environment, using in situ and in vivo experiments, landscape scale dissemination of AMR and human exposure and transmission studies. Projects are divided into three main themes: ecology, evolution, and public health perspectives. These map onto those identified in successive WHO, EU and UK AMR action plans facilitating interdisciplinary research approaches and joined up thinking.

McAllister, Tim Ph.D. Ruminant Nutrition / Microbiology, M.Sc. Animal Biochemistry, B.Sc. Agriculture

- Tim McAllister's Research and/or Project Statements: Antimicrobial resistance (AMR) in livestock from a One Health perspective, strategies for mitigation of E. coli O157:H7 throughout the beef production chain, including bacteriophage therapy, passive immunotherapy, electrolyzed

oxidizing anode water, management strategies, and dietary interventions. Interactions of microbiomes in food safety, feed quality and enteric methane emissions. Development of methods to characterize and reduce greenhouse gas emissions from beef cattle production systems in enteric methane emissions, and the implications of land use change for carbon sequestration and biodiversity in beef cattle production systems. Characterization of the digestive properties of cereal grains and the use of by-products in beef cattle diets and development of methods to enhance the ensiling of cereal forages and that value of low-quality forages. Prevention of pasture and feedlot bloat in cattle; composting as a means of disposal of animal carcasses for containment of biohazardous agents; assessing the fate of transgenic DNA ingested by livestock in genetically modified crops used as feeds; characterization of effects of tannins on cellulose digestion by ruminants; potential uses of plant extracts and probiotics as alternatives to antibiotics in livestock production. His collaborations have generated over 800 peer-reviewed scientific publications.

McCoy, Kathy Ph.D. Immunology

- Professor Kathy McCoy obtained her PhD in Immunology from the Malaghan Institute of Medical Research, Otago University, Wellington, New Zealand. She performed her postdoctoral studies and was a junior group leader at the Institute of Experimental Immunology in Zürich, Switzerland. In 2006 she joined McMaster University as an Assistant Professor where she held a Canada Research Chair in Mucosal Immunology. From 2010 – 2016 Kathy McCoy was an Assistant Professor in Mucosal Immunology in the Department of Clinical Research, University of Bern in Switzerland. In Sept. 2016 she returned to Canada and is now a Professor in the Cumming School of Medicine, University of Calgary where she continues her research on host-microbial interactions with a focus on early life. Key Areas of Expertise: Microbiome, Immune System, Mucosal Immunology

Reyher, Kristen BSc(Hons) DVM PhD FHEA MRCVS

- Kristen Reyher is Professor of Veterinary Epidemiology and Population Health at the Bristol Veterinary School, University of Bristol. She has worked in livestock practice in three countries, and holds a doctorate of veterinary medicine from Cornell University as well as a PhD in veterinary epidemiology from the Atlantic Veterinary College in Prince Edward Island, Canada. Kristen currently leads an interdisciplinary research group (the AMR Force) focussed on Antimicrobial Resistance with more than £10 million of funding from public sources as well as charities and industry. She also directed the first studies applying a counselling style called Motivational Interviewing to veterinarian-client communication. Kristen was the principal investigator for the Global Resource for Online Evidence-based Veterinary Medicine Learning project which produced the widely used EBVM eLearning site ebvmlearning.org, and is involved in EBVM on many levels. Her past accomplishments include successfully organising the data collection platform for Canada's largest livestock research effort through the Canadian Bovine Mastitis Research Network and she is interested in making research more accessible (and accomplish-able) to veterinary practitioners worldwide.

Topp, Ed Ph.D. Microbiology, M.Sc. Microbiology, B.Sc. (Agriculture) Microbiology

- Ed Topp is a Principal Research Scientist at Agriculture and Agri-Food Canada. Current research and/or projects: Assessment and management of environmental and human health risks associated with agricultural organic fertilizers of animal, poultry, and human origin: Fate and impacts of pharmaceuticals, microbial pathogens, and antibiotic resistant bacteria in food animal and crop production systems. Research and/or project statements: Mitigating Antimicrobial Resistance in food production systems, Genomics Research and Development Initiative on Antimicrobial Resistance [GRDI-AMR]

e) Workshop Presentations -- Summary Notes

(With opportunities (**O**) noted)

LINK to video recordings

8:10 Dame Sally Davies, UK Special Envoy on AMR

Keynote Presentation

Burden posed by AMR today and in the future (current trajectory) is immense

- Globally, AMR kills 700,000+ people annually; 2050 prediction is 10M deaths @ cost of US$100T.
- In Canada, first line resistance already causes 5,400 deaths and GDP loss of $2M annually (PHAC report).
- Upcoming IHME GRAM report finds burden is likely much higher. **O**: Similar study in animals and environment.

Environmental contamination with antibiotics and the impending "silent" tsunami of AMR

- 65% of 711 samples taken from world rivers (72 countries across six continents) were contaminated with antibiotics; 1 in 7 sample levels deemed unsafe by today's standards (University of York, 2019).
- Antibiotic resistant bacteria reported in Salish Sea harbour seals and porpoises (Washington State University, 2021); stranded whales, dolphins and porpoises (University of the Philippines, 2018); green sea turtles (~1/3 of samples multidrug resistant) (James Cook University, 2017); Galapagos giant tortoises living near human settlements (Charles Darwin Foundation, 2020) **O**: Tortoises as bio-indicators of ecosystem health.
- "Beach Bums" (surfers) antibiotic resistant gut bacteria 3X's more likely (University of Exeter, 2018).
- Marine microplastics litter may transport antibiotic resistant bacteria (Queen's University, 2020).

Antibiotics are critical infrastructure for all our systems, but judicious use is paramount

- Globally, >80% of antibiotics are used in farming, rather than human patients.
- Estimates point to a 67% increase in global consumption of antibiotics 2010 – 2030.
- FAIRR ranked 70% of largest protein companies (worth $338B) "high risk" for antibiotic stewardship.
- Reducing antimicrobials: UK antibiotic sales halved since 2014 and productivity maintained; usage data helped British Poultry Council see a 76% reduction (2012-19); Thailand governed use of antimicrobials in aquaculture, which resulted in fewer AMR genes in fish ponds compared to Bangkok canals (Newcastle University, 2021); InnoVet-AMR projects (e.g. nanobubble technology in SE Asia aquaculture) to minimize misuse of antibiotics.

Job of scientists to help leaders and decision makers untangle complex global challenges (like AMR)

… not by telling them what to do but rather by enticing politicians and the public to listen to case studies, ideas for intervention and evidence to inform policy. And bringing cutting edge research to the fore to make a difference in action, through policy, and delivery is best done when we all work together.

- A fully integrated One Health approach to AMR is required. National Action Plans for AMR are backbone of a multisectoral response (135 country plans so far + 50 in progress BUT need funding and implementation)**.** UK Fleming Fund helps countries develop their own sustainable surveillance systems, which benefits them but also helps protect our countries too. This type of thinking underpins The Trinity Challenge – a coalition aiming to better protect the world against health emergencies, using data-driven research and analytics. See 2021 winners. AMR challenge soon (seeking funding). **O**: Complement efforts with innovation in safe and effective alternatives to antimicrobials. **O**: More evidence and

surveillance in environment and agricultural (entire food chain) (e.g., PATH-SAFE, UK-Argentina partnership), plus a better understanding of impact of reservoirs for antibiotic residues.

- Private sector has important role to play**.** **O**: Clean up and transform food systems to be more resilient, sustainable, and equitable – realize 2030 Sustainable Development Goals (SDGs) relating to food security, improved nutrition, sustainable agriculture, and health coverage. Examples: At 2020 World Economic Forum, 14 major investors (combined assets >$7T) committed to incorporating AMR into their standards and investment decision making; 6 of 10 leading UK supermarket companies have banned routine use of antimicrobials in their food supply chains; Maple Leaf Foods (Canada) invested in establishing national network of vertical farms (400 X's more productive than ordinary farms and no pesticides, herbicides, or fungicides).
- Ensure AMR is at heart of conversations and advocate for transforming systems (human health, animal food, environment, ecosystems), surveillance and monitoring of antimicrobial use and resistance, and increasing internal and external mobilization of financial resources: UN Conference of the Parties (COP26), WHO Global Leaders Group (GLG, learn from IPCC experience) , UK G7 (June 2021), etc.
- Empower researchers everywhere by ensuring that data is open and accessible and support younger generations and researchers. All of us have a responsibility to turn numbers and ideas into meaningful and sustainable action. It's possible and there is hope -- look at all the innovation and collaboration that occurred relating to COVID-19.

8:40 Presentations related to Antimicrobial Use (AMU) and Antimicrobial Resistance (AMR) within reservoirs of AMR: farm animals, on farm, and wider environments

8:42 Tim McAllister, Agriculture and Agri-Food Canada

Antimicrobial use and resistance in Canadian Livestock (Poultry, swine, and cattle)

AMR and AMU in Canada – Current Status and One Health Approach

- 26% of infections were resistant to first line antimicrobials used (2018) and that's expected to rise to 40% by 2050 (= 300K deaths, $120B in hospital expenses, $250B GDP loss).
- In 2018, 78% of antimicrobials sold were intended for production animals (see CIPARS 2018: Integrated Findings); Compared to 31 European nations, which places Canada as 6th highest (see p.85 CARSS Report – Update 2020). Aside: variation in antimicrobials used across livestock species (treatment, feed) results in variation in AMR patterns (Huber, 2021, CIPARS reports). **O**: Characterize ecology and changes in bacterial populations resulting from changes in AMU.
- One Health pillars: 1) Surveillance, 2) Stewardship, 3) Prevention & Control, 4) Research & Innovation.
  - The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), created in 2002, is a national program dedicated to the collection, integration, analysis, and communication of trends in antimicrobial use and resistance in selected bacteria (Salmonella, Campylobacter and E. coli.) from humans (Public Health Agency of Canada (PHAC)'s Canadian Antimicrobial Resistance Surveillance System (CARSS)), animals (farm, abattoir, veterinary practices), and animal-derived food sources (retail) across Canada.
- Categorization of antimicrobials, based on importance (I-Very High, II-High, III-Medium, IV-Low, Uncategorized) in 2009 remains key in tackling AMU and AMR (see p. 9 AMU Strategy, 2018). Much of 2014-2018 reduction in AMU has been volunteer in nature, by industries themselves (also shifting to lower Category Antimicrobials). **O**: Further promote voluntary reduction in AMU in agri-systems.

The Science of AMR

- **How it spreads**… Bacteria can acquire AMR through mutations in the genome or horizontal gene transfer (HGT). The HGT of large numbers of AMR genes intra/interspecies within the microbiome of humans and production/companion animals usually involves mobile genetic elements (MGEs). Resistant bacteria develop in the guts of people and animals treated with antibiotics, which is then spread through direct contact, waste management practices and consumption of contaminated foods (see p.14 diagram in Antibiotic Resistance in the United States, 2013). **O**: Further research role of MGEs in transfer of AMR across One Health continuum.
- **Resistant bacteria are niche specific**… Surveillance of Enterococcus (E.) reveals distinct AMR diversity across a One-Health continuum (Zaheer et al., 2020). E. hirae associated predominantly with cattle, E. faecium and E. faecalis associated predominantly with humans. Surprisingly, there's more E. faecium and E. faecalis in beef processing plant than E. hirae! So, associations aren't always obvious. Sampling across environmental interfaces is also critical (Zaheer, et al., 2019). **O**: Undertake true One Health studies to ascertain associations between human/animal/environment and bacterial populations.
- **Relationship between AMU and AMR complex**… Although fewer AMR genes in natural beef production systems vs. conventional (with higher AMU), AMR bacteria still exist. So, removal of antimicrobials doesn't necessarily result in complete removal of AMR genes. **O**: Further investigate relationship between AMU and AMR.

Canada-UK potential collaborations

- **O**: Take advantage of differences in livestock AMU practices to address AMR hypotheses; **O**: Explore livestock waste streams as indicators of animal health and AMR; **O**: AMR in integrated crop-livestock systems; **O**: Share biological samples and data; **O**: Collaborate on bioinformatics/machine learning approaches to AMR ecology; **O**: Investigate animal welfare and social consequences of changes in AMU practices; **O**: Coordination in regulatory/policy decisions on AMU.

9:00 Kristin Reyher, University of Bristol

Antimicrobial use and AMR on farm and in the near-farm environment -- Known Unknowns

AMR and AMU in the UK – Current Status and Ensuring a Better Future than Predicted Globally

- In UK, 3X's more antibiotics used to treat people than animals (on kg for kg basis) RUMA 2020 report BUT global livestock antibiotic use expected to increase 67% by 2030 (PNAS 2015)! Not a certainty (yet). Hopeful UK stories: 50% reduction in antibiotic sales since 2014, and use of highest priority antimicrobials continues to decrease (UK-VARSS 2020). Tag line for antimicrobial use: "As little as possible but as much as necessary".

Reduction in AMU doesn't equal concomitant reduction in AMR – why?

- OH-STAR project aims to identify whether transmission of AMR from animals to people is a significant source of carriage of AMR in people. Followed 53 dairy farms for 2 years looking at AMR but didn't find straightforward association with AMU. **Findings**: most AMR seen in young animals (intramammary antibiotics given to cow pre-partum); AMR was less on pastureland vs. dairy housing. **Implications for surveillance**: Insist on "sameness" in sampling (same farm, same animals, same sites, same climatic conditions, same sampling technique) and recognize necessity of multiple, longitudinal sampling (Schubert, et al., 2021). Also found easy way to profile AMR on farms: researcher/vet/other

walk around in over-boot-socks and then examine microbe populations on over-boot-socks at lab. **O**: Investigate possibility of using antibiotics prescribed to treat sick animals AND modify AMR on-farm.

Global unknowns and approaches

- See Booton, et al., 2021 to illustrate some of global unknowns regarding AMR. **O**: How much does AMU drive AMR? Stakeholder practices and beliefs have an impact on-farm (Hockenhull, et al., 2017) and we need to better characterize magnitudes also. **O:** Is AMR mechanism-specific and organism-specific? **O**: What factors (include crops too!) contribute to selection and transmission of AMR? (Quantifying factors will aid in prioritizing interventions and refining policy)
- Projects: One Health Drivers of Antimicrobial Resistance in Thailand (OH-DART; reported vs. actual use differ ((garbage) bin audits helpful – idea from Canada's Saini, et al., 2012), Future-proofing Antibacterial resistance Risk Management Surveillance and Stewardship in the Argentinian Farming Environment (FARMS-SAFE). **O**: Compile a *Vade Mecum* (handbook) listing all antimicrobials used (and licensed for use in named species).

Stewardship is a shared responsibility – metrics, benchmarking, and data Integration are important

- AMU and AMR stewardship is a shared responsibility – use participatory approaches (policy making van Dijk, et al., 2017, farmer-led Morgans, et al. 2021, see article on The Canadian Dairy Network of Antimicrobial Stewardship and Resistance (CaDNetASR), vet-to-farmer, peer-to-peer learning, etc.) and ensure entire food chain of stakeholders (= drivers for change) participate; communication (e.g. prescribing champion for veterinary practices (Rees, et al., 2021)), social science (e.g. motivational interviewing) & interconnected software.
- Metrics: How do we measure antimicrobials? (Differences within | across industries & nations) Hannon, et al., 2020, Lardé, et al., 2020). Benchmarking (esp. year-to-year within farm) helps drive change (Mills, et al., 2018, Capper, et al. 2001). Data integration -- bringing disparate datasets together to help answer the BIG questions (progress tool: Haworth-Brockman, et al., 2021)

Driving future change – increased consumer demand for POC diagnostics and AMU/AMR facts likely

- Point-of-care diagnostics once lauded as solution to AMR (O'Neill report, 2016) but very few in pipeline – why? **O**: Develop more POC diagnostics to facilitate judicious prescribing of antimicrobials.
- Consumers may well drive change -- now possible to track antibiotic footprint (interactive guide to help understand world consumption of antibiotics) and consumers may insist on Antibiotic Facts label.

9:14 Transmission of AMR between reservoirs of AMR: in agriculture, the environment, and to humans

9:15 Will Gaze, University of Exeter

AMR evolution, ecology, and transmission: a One Health perspective

Timeline of Antimicrobial Resistance

- Today's One Health understanding has changed very little in last 45 years (contrast CIPARS diagram vs. Linton 1977), except to add that AMR selection occurs in environmental microbiome too.
- Evolutionary timeline of antibiotic and resistance (Waglechner, et al. 2021) underscores importance of visualizing microbial world in all its scales (n=5 x 10^{30}, speed of reproducing, ways of exchanging DNA) to understand problems of AMR in context (resistance is complex, not just a clinical problem). "Animal-to-human spillover of new viruses that are capable of infecting diverse host species (high host plasticity) signal emerging disease events with higher pandemic potential" Johnson et al., 2015.

Evolution, selection, and transmission of AMR

- Must consider agricultural and natural environments because there's evidence of resistance mechanisms from over 2 billion years ago! Antibiotic resistance in pathogenic bacteria is not a modern phenomenon (huge variety of Antimicrobial Resistance genes (ARGs) evident in 30,000-year-old Beringian permafrost, D'Costa 2011).
- How to address role of agriculture and environment in AMR pandemic given: (1) Gene transfer events from resistome within environmental and animal microbiomes leads to emergence of novel resistance genes in human pathogens, (2) Due to co-selection associated with genetic complexity of MGEs, all antimicrobials have the potential to drive emergence of clinically important resistance genes, (3) Mobile AMR genes have independent evolutionary trajectories to their bacterial hosts - even within a hospital setting, resistance genes are mobilised between host and plasmid type over short time frames (Sheppard et al., 2017), (4) Infections attributable to environmental antibiotic resistant bacteria (ARB) transmission (as opposed to MGE/ARG) may not occur at the time of exposure, or even in the same individual, and (5) Most transmission of clinical pathogens may occur from person - person but doesn't reduce the importance of horizontal gene transfer (HGT) from environmental or animal associated bacteria to human commensals/pathogens (analogy with SARS-CoV-2)?
- We know environment is widely contaminated with ARB associated with human activity and that resistance is transferred through fecal contamination. Experiments support hypothesis that in situ selection is also likely (Stanton, et al., 2020; Murray, et al., 2020). Selected papers of interest:
  - AMR differences between intensive and extensive Iberian pig farms linked to differences in abundance of MGEs (fewer in Iberian pig farms and ponds) (Mencía-Ares et al., 2020);
  - *C. difficile TR078* provides evidence of a highly linked transmission network between humans and animals (Knetsch, et al., 2018);
  - ESBL-E. coli and pAmpC-E.coli are resistant to important β-lactam antibiotics and a Dutch study attributed community acquired carriage of these bacteria to human-to-human transmission (2/3) but noted spread wasn't likely to be maintained without transmission to and from non-human sources (1/3) (Mughini-Gras, et al., 2019). Aside: extracting a subset of data (June-August) resulted in a re-ordering of attribution rates – in summer months, % transmission attributed to aquatic sources rose to 13% (eating seafood, swimming (Leonard, et al., 2015 re: ingestion of 3GC resistant E. coli; Leonard, et al., 2018 re: "Beach Bum Survey")).

AMR Surveillance – what to focus on?

- The effectiveness of surveillance efforts is tied to focus (what is surveilled) and subject to resource constraints. Focusing on specific pathogens (e.g. ESBL-E.coli (WHO, 2021)) will only give you a tiny snapshot of what's going on in whole resistome (a reactive approach). A more proactive approach is favoured, perhaps looking for novel resistance mechanisms or, better yet, looking at resistome level (especially at the interface of animal | environment | human) using metagenomics. **O**: Adopt a more proactive surveillance approach by monitoring resistomes (especially at animal | environment | human interfaces) using metagenomics.

9:30 Ed Topp, Agriculture and Agri-Food Canada

Challenges in Understanding AMR Transmission across the One Health Continuum

Organizing capacity to undertake research on AMR across One Health

- Genomics R&D Initiative (GRDI) was first created in 1999 to establish and maintain core genomics capacity (annual funding ~ $20M). Participating federal departments and agencies: AAFC, CFIA, ECCC, DFO, HC, NRC, NRCAN, and PHAC have a strategic research program for AMR focused mainly on food production and, more broadly, across One Health continuum. First funding for AMR was in Phase VI (2016-2021) and will continue into the next round of funding (AMR2).
- AMR2 overarching goal: To identify targets for action through mapping the development and transit of Antimicrobial Resistance through healthcare, animals, plants, and the environment to preserve the effectiveness of the antimicrobials that Canadians rely on every day**.** Project comprises:
  1) Assess drivers, reservoirs, and dissemination of AMR in environmental matrices (ECCC, AAFC)
  2) AMR in healthcare and Canadian communities including vulnerable populations (PHAC)
  3) Mitigate development and Transmission of AMR across farm-fork-clinic continuum (DFI, AAFC)
  4) Transmission of AMR pathogens to Canadians via farm-fork-clinic continuum (AAFC, HC)
  5) Leveraging genomics for risk science (PHAC)
  6) Real time detection & communication of AMR results across One Health Continuum (PHAC, CFIA)
  Aside: UK-Canada link already exists thanks to GRDI science advisory board membership (UK: Alison Mather, Will Gaze; Canada: David Bailey, Jerry Wright).

Fundamental gaps in understanding and managing AMR across One Health

- AMR today concerns exposure assessments: Amount? Type of AMR in environment or is it foodborne? How are humans exposed and outcome? How to best use knowledge gained to mandate standards or practice (=policy relevant)? **O**: Need to define hazard component for AMR risk assessment
- **O**: Validate existing food safety practices with respect to protection against AMR
- **O**: Gene level understanding of ARGs transmission & associated MGEs between microorganisms
- **O**: More research on resistance and transmission in plant-based systems (using antibiotics, antimicrobial pesticides (fungicides) and herbicides, metals (copper),) and aquaculture.
- AMU in production of fruits and vegetables differs between countries, which likely impacts AMR. **O**: Contrast UK and Canadian orchards. **O**: Compare domestic vs. imported fruits and vegetables.
- Truly integrated surveillance systems must include environmental surveillance (via sewage and farm effluent). **O**: Determine what measures to include (how best to detect and quantify) environmental surveillance and distinguish between fecal vs. non-fecal impacted matrices.

9:42 Use of genomics to improve AMR surveillance

9:43 David Aanensen, University of Oxford

Data driven genomic sequencing for AMR surveillance

About Centre for Genomic Pathogen Surveillance (CGPS) and Genomic Epidemiology

- Team of epidemiologists, software engineers, and capacity building implementation experts in various areas of genomics housed at The Big Data Institute (BDI), University of Oxford.
- Genomic epidemiology aims to distinguish cases of a pathogen (related vs. unrelated) and identify risk using genomics. That process can be carried out at different data scales (within institute … between institutes nationally, internationally, or globally).
  - Process: (1) collect samples, (2) sequence genomes, (3) compare genome sequences and determine their relatedness (often illustrated as a tree like (branching) structure with clusters of genomically similar sequences evident). The distance between any two genomes (relatedness) is, essentially, an

operational unit of genomic surveillance, (4) map information (phenotypic or genotypic record, geographic location, etc.) against clusters, (5) Deliver assessment of risk (e.g., emergence of MRSA-15 (st22) epidemic lineages was shown to coincide with the introduction of fluoroquinolones in the UK in the mid 1990's). **O**: For AMR, looking at the genomes of bugs sequenced for signatures of risk (resistance genes, mobile genetic elements, single mutations, etc.) may help predict resistance.

Technology Transfer and Ownership of Data Interpretation is Key to Successful Surveillance in LMICs

- **AMR** – Tackling Antimicrobial Resistance: Country Innovation
  - Philippines AMR Surveillance Program (Argimón, et al., 2020) -- CGPS and RITM (Research Institute for Tropical Medicine). Initially: mature (30+ years) phenotypic AMR surveillance program comprising ~30 hospitals that reported bug-drug combinations of resistance to local stakeholders (hospital, prescription, etc.) and, annually, to WHO's GLASS-AMR. Annual reports included basic graphs but couldn't explain observed trends. Working with CGPS, a functioning genome sequencing lab was established so now RITM annual reports include information on strain, the AMR gene, and delivery mechanisms (chromosome, mobile genetic element,). And, importantly, they now use genomic sequencing to spot outbreaks early (which would not have been spotted previously with their conventional phenotypic measures) and institute appropriate infection control measures.
  - National Surveillance Labs (*http://tinyurl.com/GHRUamr*) – early experience establishing sequencing laboratories in Low- or Middle-Income Countries (LMICs) spurred development of technical support packages around laboratory / bioinformatics / data flow rollouts linking genomics to epidemiology, and financial capacity building for sites to become fully sustainable and able to manage incoming funds. It's very important LMICs take ownership of technology AND interpretation of data locally so public health decisions can be made. Labs established so far: Colombia, India, Nigeria (tool: Microreact, publication: Ayorinde, et al., 2021), and the Philippines.
- **COVID-19** Genomics UK Consortium (COG-UK) – A large number of consortium partners aimed to rapidly fire up decentralized sequencing across the UK (to gain better understanding of SARS-COV-2 viral transmission and evolution, and inform public health responses and vaccine development). LARGE tree of genomes (>500K in UK COVID-19) was difficult to interpret. Distinguishing varieties of concern (alpha, beta, delta) as public health units facilitated discussion and communication. Aside: COVID-19 USA (Centre for Disease Control (CDC)) Genomics Consortium is called SPHERES.
  - COG-UK created translational tools (low level plumbing) to enable data driven pathogen surveillance and understand how SARS-COV-2 (COVID-19) was behaving, which helped bear on public health interventions (as was done in New Zealand). Tools:
    - Epicollect5: free and easy-use mobile data platform
    - Microreact: open data visualization and sharing for genomic epidemiology
    - Pathogenwatch: a global platform for genomic surveillance
    - Data-flo: open-source, modular, and extensible **data integration** (because every institute has a different data architecture, and we cannot expect to replace existing data tools, but we do want the data to flow into Epicollect5).

  Conceptually, approach to COVID-19 and AMR should be the same: determine species and assess risk. To enhance rapid firing up of genomics around AMR (as was done with COVID-19), it's important to focus on "low level plumbing" and use existing systems that can be pivoted towards AMR. **O**: Pivot existing tools to track lineages and variants of AMR.

- Bottlenecks for AMR and COVID-19 are same: data and data tools, linking genomics to epidemiology, rapid interpretation, political / supply chains, expense, etc. **O**: Address existing bottlenecks for AMR.

10:00 Rob Beiko, Dalhousie University

From Genomes to Transmission Maps in ten minutes or less

From genomes to models in 4 steps (= filling in blanks of the "confusogram")

- WANT: robust identification of key genes and mobile elements that shuffle them; predictive genotype-phenotype models; models of transmission (within "confusogram") HAVE: a wealth of genomes; info about location, time, habitat; lab-based assessments of resistance; bioinformatics applications.
- Antimicrobial Resistance Emergence Transmission and Ecology (ARETE) **pipeline** in 4 steps:
  (1) Data Processing (genome retrieval & assembly), (2) Identifying Resistance (**AMR genes**, **mobile genetic elements**), (3) Tracking resistance (phylogenomics, **gene transfer**, co-evolutionary models), (4) Modeling Resistance (**genotype** / phenotype, risk modeling). Aside: though all topics are important, yellow highlighted items were discussed in detail.
  - **AMR genes** are identified using the Resistance Gene Identifier (RGI) from the Comprehensive Antibiotic Resistance Database (CARD). Push genomes into RGI and it will output perfect matches and loose matches (recognizably homologous but not exact matches). Sometimes, when you pull in additional information, loose matches are legitimate AMR genes.
  - **Mobile genetic elements** (MGEs are sequences of genetic material that can change places on a chromosome, and be exchanged between chromosomes, between bacteria, and even between species). Genomic islands (GIs are discrete DNA segments that establish horizontally transferred genes in a population). GIs are an important component of MGEs and key agents in the transfer of resistance genes. IslandCompare is a GIs prediction tool that identifies GIs in multiple genomes, which allows for comparative genomics.
  - **Gene transfer** can be identified through a strictly phylogenetic approach. Because a lateral gene transfer event often disrupts the tree topology, rSPR software compares species tree with corresponding gene tree and unwinds differences to infer lateral gene transfer events.
  - **Genotype** to predict resistance using machine learning is something lots of people are working on. Most interested in actual features that are predictive (of resistance).

  Example of **pipeline** involving 1,273 Enterococcus faecium genomes to try and build a comprehensive picture of "who is sharing with whom, and what it means". (1) automated quality control and filtering, (2) association of RGI matches with genomes and habitats (intermingling of habitats is evident, GIs give clues about "who is sharing with whom"), (3) implied gene transfers (e.g., copper transport repressor is important), (4) if use all genes in pangenome of E. faecium, accuracy of vancomycin prediction is perfect but if you use only genes suggested by RGI (supposed to be best predictors), model accuracy is very low. Deduction: some information is missing. **O**: Determine what other features / information / genes are important in predicting resistance? Possible issues with how genes are being defined?
- Further research: **O**: Identify MGEs, still don't know what makes them tick, move around, **O**: can map transfers but can't explain large divergences and differences, **O:** Classify but don't know what important features are being lost when predictive models fail, **O:** Tying it all together – relationship between genes and MGEs, dissemination patters, and habitats?
- Current version of ARETE pipeline: https://github.com/fmaguire/arete/

f) Workshop Breakout Sessions -- Summary Notes, by Theme

THEME 1

Antimicrobial Use (AMU) and Antimicrobial Resistance (AMR) *within reservoirs of AMR*: farm animals, on farm, and wider environments

Q1 What are the unique features of Canada and UK agri-systems, natural environments, and cultures that may foster Anti-Microbial Use (AMU) and Anti-Microbial Resistance (AMR) in farm, farmed animals, and wider natural environments?

Farming systems in the UK and Canada differ in several ways. In the UK it is more common to have smaller farms, free range livestock, and farms with multiple species. The UK has more sheep farming. Beef in the UK is usually grass fed and there is little in the way of feedlot beef farming. In contrast, Canadian farms are more likely to be large, single-species and intensive. In both Canada and the UK antibiotics for livestock are obtained by prescription in both settings, rather than over the counter. Regulation of antibiotics differ between the two countries, for example, the UK uses more fluoroquinolones while Canada still allows the use of ionophore antibiotics (monensin and lasalocid) as growth promoters in cattle. It should also be noted that there are differences within the two countries, in terms of provinces in Canada and devolved administrations in the UK that create differences in regulatory landscape. The UK does not use antibiotics on crops, whereas in Canada antibiotics are applied directly to orchards. However, groups agreed that more work needs to be done to gain a comprehensive picture of farm management practices and regulations in the two countries. Antibiotics for growth promotion was banned in the UK in 2006 as part of an EU directive; this practice was banned in 2018 in Canada.

Q2 What are the research needs, gaps, and opportunities for implementing alternatives to antimicrobials and reducing selection and transmission within AMR reservoirs in farms, farmed animals, plants, and wider natural environments? Please take into consideration cross-discipline research opportunities bearing socio-economic and behavioural drivers in mind.

There are large gaps in the knowledge about farm management practices and the drivers of AMU in agriculture; incorporating economic modelling and involving social scientists will be important here. Living labs, where stakeholders, such as representatives from government, academia, funding bodies and industry may facilitate interdisciplinary collaboration required to tackle the issue. For example, economic barriers to vaccine uptake which subsequently drive AMU is a problem particularly in LMICs. Microbial pathogens other than bacteria also represent a knowledge gap despite the burden they represent. For example, parasites represent a significant problem in aqua/agriculture and the emergence of parasiticide resistance is worrying. Fungal pathogen resistance to antifungals is increasingly problematic in the UK. More work needs to go into uncovering the precise relationship between AMU and AMR. Reduced AMU in the UK has not resulted in a corresponding reduction in AMR. We also need to better understand the relationship between different farm settings and AMU; for example, it does not seem to be the case that small free-range farms have less AMU and lowered AMR, although this relationship is often assumed. The role of inter-species transmission of AMR is also poorly understood, as well as directionality. AMR spreads

from animals to humans, but there is also transmission from humans to animals; this directionality is often left out of "confusograms" (see Figure 1). Unintended consequences of policies and regulations in agriculture also need to be considered. For example, bismuth in milk has caused problems in cheese manufacture, resulting in cheese producers being unwilling to purchase milk from dairy farms where bismuth has been used. Likewise, pursuing green policies to reduce CO2 emissions has driven systems to be integrated to improve efficiency, but the risk that this poses on the emergence and transmission of AMR has not been considered. Both the UK and Canada have dispensing records of antimicrobials that quantify usage – these are useful resources. Developing imaging of gut microbiome to observe interactions with probiotics would be a useful technological development. There is a need to understand the innovation or technological bottlenecks that are obstructing the development of farm-suitable rapid point of care diagnostics. There is strong appetite from farmers, academics, and veterinarians for these, but the demand is not being met by products in the pipeline.

Q3 Considering the above-mentioned capabilities and research needs, what are the key bilateral partnership opportunities between Canada and the UK?

It will be important to gather comparative data from the two agri-systems to identify differences and similarities. This is needed at the farm level, but also up to understanding higher-level regulatory and consumer-led factors. Understanding of management practices is very important to ensure that 'low hanging fruit' approaches to reducing AMU and AMR have been utilised. This is part of recognising that in many respects, the problem is not so much AMU or AMR, but a health systems problem. We also need to understand why AMR is not reducing in response to AMU. Identifying the drivers of AMR emergence and spread at the farm is hugely important: levels of antimicrobials in the farm environment, species mixing, and the impact of seasonal workers. Precision phenotyping and genomics approaches to identify the presence of AMR genes and phenotypic AMR.

THEME 2

Transmission of AMR *between reservoirs of AMR*: in agriculture, the environment, and to humans.

Q1 What are the unique research and innovation strengths (incl facilities and infrastructure) in Canada and UK in addressing AMR transmission between AMR reservoirs in agriculture, the natural environments, and humans?

Both nations have developed/are developing AMR surveillance programs. The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) is globally recognised and monitors trends in AMU and AMR in selected bacterial organisms from human, animal, and food sources across Canada. In the UK, the veterinary medicine directorate (VMD), the animal and plant health agency (APHA) and the Environment Agency monitor AMU in agriculture and AMR in the food chain. Recently, Public Health England (PHE), and the food standards agency (FSA) have been awarded £20mil to scope One Health surveillance program, encompassing animals, humans, and the environment. Canada has the Genomics Research and Development Initiative which acts on the federal level to build understanding of AMR in human, animal, and environmental settings, and to inform strategies that would preserve effectiveness

of antimicrobials currently in use. It was noted that UK farmers tend to be quite open to researchers coming on farm to collect samples; this is less likely in Canada. Both countries have lots of data and sample collections from research and surveillance activities, but analysis may be a bottleneck. Both also have developed thinking around the one health model. The UK has a strength in animal models of transmission and AMR emergence, and there is also programme into the development of antifungals at NIAID. Canada has the AMR Network that coordinates stakeholders around the one health project.

Q2 What are the research needs, gaps, and opportunities for implementing alternatives to antimicrobials and reducing selection and transmission between AMR reservoirs in humans, animals, plants and natural environments.

As well as developing alternatives to antimicrobials such as vaccine, phage therapies, probiotics, and CRISPR-Cas9 technologies, there is a need to build an evidence base confirming effectiveness. They must also be cost effective for there to be uptake among farmers. A more thorough understanding of what is driving AMR: the role of minimum inhibitory concentrations, or AMR in the presence or absence of infections. Further, surveillance programmes tend to focus on specific problem pathogens. However, the wider microbial population needs to be investigated if we are to learn more about transmission pathways. Surveillance also often provides qualitative metrics: presence or absence of an organism or an AMR gene. Instead, quantitative measurements of densities of microbes and genes is required. Identifying hotspots of transmission to inform strategies to reduce spread, genomic tools are critical. The role of the gut microbiome in the transmission of AMR is of interest, particularly whether colonisation of the gut by an AMR organism is necessary for AMR to be transmitted in this context. Similarly, the effect of antimicrobial residues in waste (such as waste milk or slurry) on AMR in the environment is unknown. Rapid diagnostics at the point of care could provide an important tool to identify significant veterinary pathogens – the treatment of these being the main driver of AMU and AMR in the agricultural setting. There is little understanding of how different AMU practices and regulations on the international scale may influence what you observe in any one place through vectors such as migratory birds, which may ingest antimicrobials, or antimicrobial residues, or AMR microorganisms, and then spread these to other nations.

Q3 Considering the above-mentioned capabilities and research needs, what are the key bilateral partnership opportunities between Canada and the UK? Please consider cooperation across areas covered by existing national interventions and areas where entirely new research is needed. How can research outcomes in these areas influence potential government policy and regulation in the UK and Canada?

The impact of the built environment and interspecies interactions on AMR is a gap in the knowledge. Several attendees talked about a UKRI-CIHR programme which facilitated exchange of ECRs; this was considered very successful, but it was commented on that it was allowed to peter out. Delegates suggested that sustained investment and partnership is necessary, with a strong emphasis on inter-disciplinary AMR training. Existing infrastructure for partnership includes JPI AMR, and there is an MOU in place between veterinary drugs directorate (VDD) in Canada and the UK Veterinary Medicines Directorate (VMD). The latter provides the opportunity to share regulatory and policy information from both sides. TATFAR task force (transatlantic) also provides source of engagement. Soil culture collections

in the UK are an important to understand transmission. Point of care diagnostics would also be welcome. Expanding the learning and developments in environmental sampling from the RAPTOR covid19 project in the UK. Sharing of genomic and phenotype data and using this to develop artificial intelligence and machine learning tools to better predict phenotypic AMR necessary. Standardisation of data and analysis methods, as well as understanding of differences in nomenclature, would aid collaborative efforts.

THEME 3

Use of genomics to improve AMR surveillance

Q1 What are the unique research and innovation strengths (incl facilities and infrastructure) in Canada and UK in genomics that can improve AMR surveillance systems?

The UK has demonstrated a strength in rapidly organising a huge network to coordinate decentralised sequencing combined with standardised and centralise processing and analysis. This should be exploited in tackling AMR. Canadian delegates agreed that this was a particular strength of the UK and that it would have been very difficult to do in Canada. Centralised data processing under a shared analysis framework is important for repeatability. In the UK, APHA uses a standardised approach for establishing resistance at phenotypic level national surveillance and is beginning to move into incorporating genotypic analysis. CIPARS in Canada has also produced a huge dataset from across the food chain. There are lots of analysis opportunities with these large datasets.

Q2 What are the research needs, gaps and opportunities involving genomics for implementing alternatives to antimicrobials to reduce selection and transmission of AMR in humans, animals, plants, and the environment?

Discussions in breakout rooms emphasised the need to standardise methods, in sampling as well as analysis. There may be difficulties in data sharing due to sensitivities of the data, but this may be addressed by standardised processing and analysis methods so that results are comparable. Delegates talked about the need to expand microbiome work; currently, AMR seeding events may be completely unknown - you can't quantify from a population you haven't sampled. This would be important for understanding the genomic context within which AMR may emerge and then rapidly spread throughout a population. Standardisation of sample collection was also discussed, and the fact that variations here can limit the potential for meaningful integration of resulting data. Prospective sequencing, environmental surveys are important, but also understanding how organisms and genes are moving around and the role of vectors; this would benefit from the involvement of colleagues across disciplines, particularly those in the social sciences with behavioural expertise. Both Canada and UK have historical collections of pathogenic microbes from before the discovery and widespread use of antimicrobials. Specific collections mentioned were the Murray Collection, the National Collection of Pathogenic Fungi (both UK) and CABI. These represent an under-utilised resource that could aid with understanding horizontal gene transfer and phenotype emergence. Using artificial intelligence (AI) and machine learning (ML) was discussed to bridge the genotype to phenotype gap, to recreate wet lab analysis, and data

integration. Improvements in in silico methods is required to avoid experimental bottlenecks. The question of whether we should be tracking organisms or plasmids has not yet been addressed.

Q3 Considering the above-mentioned capabilities and research needs, what are the key bilateral partnership opportunities between Canada and the UK? Please consider cooperation across areas covered by existing national interventions and areas where entirely new research is needed. How can research outcomes in these areas influence potential government policy and regulation in the UK and Canada?

Parallel longitudinal studies that could incorporate stratified sampling would be very valuable. Building in silico AI/ML tools to aid with genome to phenotype prediction, and perhaps to integrate data following sampling. Developing methods for plasmid epidemiology could help fill in blanks of the 'confusogram' which are not well represented by epidemiology at the organism level. There could be an interesting opportunity to construct 'meta' AMR databases from existing databases, such as CARD and PhA4ges. Thorough descriptions of sampling would be very valuable for such projects, and, where possible, the standardisation of sampling methods. Cooperation on standardisation of analysis pipelines would also be welcome, for example, by utilising CLIMB across UK and Canada. A participant also highlighted through the BBSRC IPA scheme there is already a bilateral collaboration with Canada on AMR.