

A One Health genomic approach to antimicrobial resistance is essential for generating relevant data for a holistic assessment of the biggest threat to public health



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Antimicrobial resistance (AMR) threatens modern medicine as we know it. AMR infections may ultimately be untreatable and routine surgeries will become inherently risky¹. By 2050 more people may die of drug-resistant infections (DRIs) every year than of cancer, which equates to more than 10 million annual deaths globally² and the World Bank has estimated that AMR could cost the global economy \$1 trillion every year after 2030. DRIs also lead to an increase in the length of hospital stays, the use of more toxic or costly antibiotics and an increased likelihood of death³. BRIC nations (Brazil, Russia, India, China) and socio-economically challenged countries and people who already have higher rates of infectious diseases will feel the greatest impact². Indeed, AMR has been likened to the 2008 global financial crisis on an annual repeat cycle. That is because the effects of AMR are not just confined to the human medical sector. The veterinary sector is also reliant on the availability of antimicrobials to treat infectious diseases in companion and food-producing animals.

The level of concern around AMR was reflected at the United Nations General Assembly in September 2016. In early 2018, the World Health Organization (WHO), the Food and Agricultural Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), signed a Memorandum of Understanding⁴ to step up joint action to combat health threats associated with interactions between humans, animals and the environment with a strong focus on AMR. This approach is termed One Health

because it recognises that the health of people, animals and the environment is intimately connected. From a climate perspective, higher than average temperatures can exacerbate AMR as pathogens expand into new regions. Similarly, extreme weather events such as flooding and droughts, which impede sanitation efforts, can increase its spread.

Globally, there has been a surge of action to reduce the threat of AMR. This includes new schemes and funds to incentivise the development of new antibiotics and public and health sector campaigns that aim to reduce unnecessary and inappropriate prescribing of antimicrobials in the human and veterinary sector. Bacteria are consummate travellers and are extremely adept at passing on their genetic 'cargo' containing genes that confer antibiotic resistance to other bacteria. We know very little about the levels of circulating drug resistance in water or non-human AMR reservoirs, thus knowing what, where and when to apply potential solutions is part of the challenge in tackling AMR. It is understood, however, that the information is country-specific and dynamic: it will change from year to year, vary across a region and is inevitably increasing.

Regions north and west of Australia including Indonesia, China, Russia, Africa, India and South and East Asia more broadly, as well as regions within South America, are recognised hotspots where mortalities and morbidities are expected to be greatest². From a geographic standpoint, Australia, perhaps more than anywhere else, has an opportunity to introduce a robust, state-of-the-art genomic surveillance system for tracing and tracking AMR and

pathogen evolution from a One Health perspective. As an island nation with globally recognised biosecurity and modern antimicrobial stewardship practices that cannot be introduced retrospectively in other regions, it is anticipated that sophisticated surveillance will offer significant savings to our burgeoning healthcare budget – expected to hit 15% GDP by 2040⁵ – well in excess of the cost of its set up and ongoing maintenance.

To date, the lens applied to AMR has focussed on pathogenic bacteria found in hospitals and healthcare facilities. But buried beneath, at a much higher resolution, is a need to understand the genetic vectors that purvey AMR genes (ARGs) and virulence genes without the separation between disease-causing and commensal bacteria. This bacterial ‘community’ level understanding can then be overlaid onto the broader picture that considers interlinked environmental compartments in their broadest sense including human and animal gut microbiomes, rivers, soils, wastewater, and so on (Figure 1).

ARGs are located either chromosomally or extra-chromosomally and may be associated with mobile genetic elements such as plasmids, integrons, gene cassettes, insertion sequences, or transposons. These are the vehicles that enable vertical and horizontal gene transmission (HGT) allowing susceptible bacterial strains to become resistant⁶. Collectively this is referred to as the mobile ‘resistome’⁷. Knowing which bacteria possess a resistome (intrinsic and mobile) is therefore key to a comprehensive, robust and scientifically-defensible AMR surveillance system and to the development of new mitigation strategies.

A recent analysis of the mobile resistome in more than 23 000 bacterial genomes showed that mobile ARGs are predominantly carried by four bacterial phyla (Proteobacteria, Firmicutes, Bacteroidetes and Actinobacteria). The greatest concentration of ARGs localise within the Proteobacteria, the group that contains Gram negative genera that includes *Escherichia*, *Salmonella*, *Vibrio*, *Helicobacter*, *Yersinia*, and *Legionellales*. In addition to bacterial

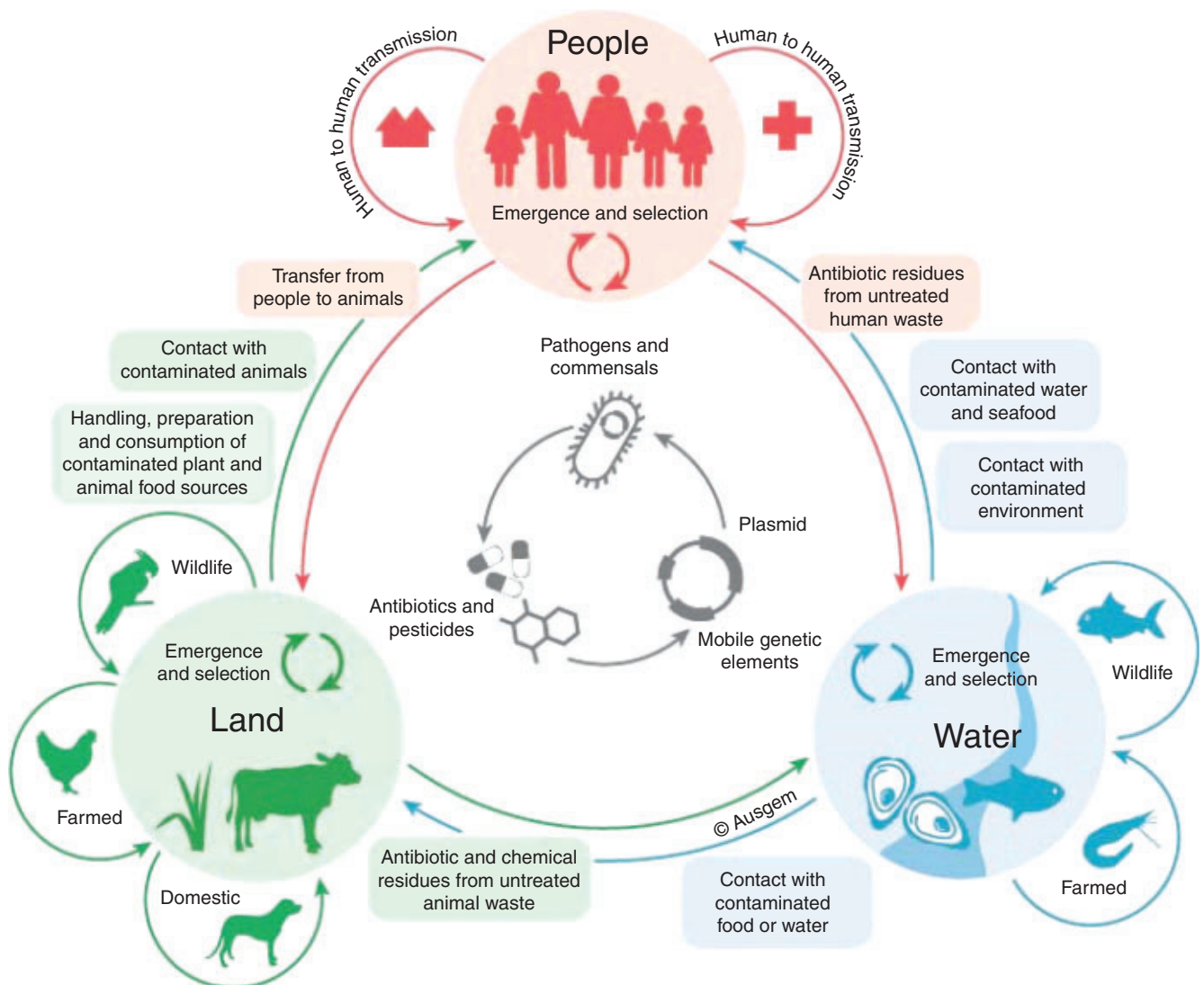


Figure 1. One Health system diagram showing the spread of AMR.

phylogeny, ecological barriers, although poorly understood, influence how mobile elements move and where they reside⁷.

AMR is not a new nor a man-made phenomenon. Our clinically important antibiotics are largely derived from natural compounds and, as such, bacteria have evolved to survive in their presence. The advent of large scale manufacturing of pharmaceuticals and their widespread use in medicine, veterinary practice and intensive agricultural settings has exponentially increased the selection pressure whereby all bacteria – commensals and pathogens – are more likely to possess ARGs.

A significant proportion of antibiotics are excreted unmetabolised into the environment and many will make it past our sewage treatment plants and into our waterways. This has ramifications for safe fresh food production, which can also be adversely affected by the use of organic fertilisers on farmland⁸. Selection pressures afforded by antimicrobial residues from industrial, agricultural and wastewater sources enable the amplification, maintenance and spread of antibiotic-resistant bacteria and ARGs. Active stewardship in all sectors is needed to avoid gene flow to and from environmental resistance reservoirs but while antimicrobial stewardship will delay and confine AMR, indirect selection and cross resistance can still occur. Resistance mechanisms to biocides and heavy metals, such as copper and zinc which are used as non-antibiotic growth promoters in intensive animal industries^{9,10} and in other settings, may be present on the same genetic elements as those conferring resistance to antibiotics.

Perhaps of greater concern is the high frequency of insertion sequences such as IS26, that are remarkable in their ability to capture, mobilise and shape the resistance gene cargo^{11,12} – they are primed to pick up ARGs, which includes clinically-relevant antibiotics. The behaviour of IS26 may influence the overall fitness imposed to the bacterial hosts that carry these elements by inadvertently deleting DNA sequences in the core plasmid backbone that influence fitness¹³.

One of the biggest gaps in knowledge is quantifying carriage and long-term maintenance of AMR in the gut of healthy humans. Carriage rates are influenced by contact and consumption of water, antimicrobials, and food and the environment more broadly, which includes wildlife and companion animals. *E. coli* is a model organism that colonises a range of environments, can be considered a commensal or pathogen in all vertebrates, and is therefore widely used as an indicator of faecal contamination in municipal water supplies.

HGT has enabled *E. coli* to evolve both as an intestinal and an extraintestinal pathogen and both clades have acquired resistance to multiple antibiotics. Our whole genome sequencing has enabled

us to understand ARG carriage in commensal and pathogenic *E. coli* populations in swine, poultry and humans and how it moves between these reservoirs. Antibiotic residues also act as an AMR selection pressure in wildlife populations that cohabit regions where anthropogenic activities are high.

More recently, *E. coli* from the gastrointestinal tracts of 40 per cent (80 birds) of the sampled silver gull populations nesting on Five Islands near Wollongong in NSW were found to carry *E. coli* containing a carbapenem resistance gene. Specifically, *bla*_{IMP-4}, found within the cassette array *bla*_{IMP-4}-*qacG*-*aacA4*-*catB3* of class 1 integrons, was detected in phylogenetically diverse *E. coli* that share many features with *E. coli* from humans causing serious infections in Australian hospitals. These studies show that the use of antibiotics can have a significant impact on the environment and on wild animals¹⁴. While this is a significant example of transmission of ARGs with local relevance, it highlights the universal challenges of controlling and curtailing the impact of AMR.

In this era of globalisation, Australia needs technologies that will enable us to adapt and minimise the unprecedented risk of AMR. Fortunately, we have the technology to be a leader in One Health surveillance of AMR. This approach will help us to make data-driven decisions around targeted antibiotic use (in livestock and people), outbreak risk (including the source of infection), and assist us to get a handle on emerging resistance via known and (currently) unknown mechanisms.

The UN Interagency Coordination Group on Antimicrobial Resistance (IACG; includes the WHO, the FAO and the OIE) is in the process of formulating its final recommendations to ensure the world's leading organisations address the threat of AMR. This will feed into the UN Secretary General's report that is due in September 2019. The report will aim to provide practical guidance for better coordination effective global actions. It won't be a moment too soon.

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

Professor Steven Djordjevic heads the Pathogen Proteomics and Genomics research group in the iThree Institute at the University of Technology Sydney (UTS). He is also the UTS research lead for AusGEM (Australian Centre for Genomic Epidemiological Microbiology); a collaborative research partnership between NSW Department of Primary Industries and the University. His team's research focuses on bacterial pathogenesis and antibiotic resistance from a One Health perspective, which recognises that the health of people, animals and the environment are interlinked.

Dr Branwen Morgan, PhD, MAICD began her scientific research career working on a pine tree fungal pathogen before moving into molecular neuroscience for her PhD, which was conducted at Sydney's Garvan Institute of Medical Research. She left research for a career in strategic communications and project management in the science not-for-profit and pharmaceutical industry sectors. Branwen has worked as a journalist, chaired a number of public forums for Nature (research translation and innovation and open data) and the Australian British Chamber of Commerce, and is a Science Technology Australia Board member. She holds an honorary appointment as a visiting fellow at UTS where she also manages AusGEM, a research partnership between the university and the NSW Department of Primary Industries.



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