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Antibiotics in the environment: sources and consequences

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The production of antibiotic chemicals and resistance to these chemicals are ancient survival strategies of bacterial species living in complex and competitive natural environments. However anthropogenic activities such the release of active and partially metabolized antibiotics into the natural environment may contribute significantly to the current global health crisis of antibiotic resistance. Every year thousands of tonnes of antibiotics are administered to humans and animals, 70- 90% of which are released unchanged in waste. Whilst manure and waste water treatments are effective in removing pathogens they are generally ineffective at removing antibiotic residues. In addition waste products contain antibiotic resistant bacteria and antibiotic resistance genes selected for in the gastrointestinal tracts of humans and animals treated with antibiotics. Treated and in many countries untreated waste products are used as crop and pasture fertilizer or may simply be disposed of in waterways. Antibiotics have been detected in most environmental media including soil and surface, underground and coastal water and sediment. Even at sub therapeutic concentrations antibiotic residues promote antibiotic resistance as bacterial populations evolve by mutations and/ or horizontal gene transfer. Identical antibiotic resistance genes and insertion sequences have been found in environmental bacteria and clinical isolates implicating the environment as a source of antibiotic resistance in pathogenic bacteria. Humans and animals are exposed to antibiotic resistant bacteria and antibiotic resistant genes in water, pastures, forage crops and vegetables.

The aim of this review is to provide an overview of the literature on the topic of anthropogenic antibiotic contamination in the environment and the causes and consequences of this contamination.

Antimicrobial use and resistance in plant based agriculture

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Bactericides, fungicides and other plant protection products play an important role in the management of plant diseases. However, their use can result in residues on plants and in the environment with detrimental consequences. Use of streptomycin and oxytetracycline is correlated with increased resistance among these plant pathogens to these agents. Resistance to copper compounds and other fungicides is also frequently observed. Importantly genes can be exchanged among a variety of bacteria in the plant production environment and in the food chain. Through co-resistance, cross resistance and gene up-regulation, resistance to one compound may confer resistance and multi-drug resistance to other similar or even very dissimilar compounds. Given the alarming and global rise in antimicrobial resistant organisms worldwide and their effects on plant, animal and human health, the prudent use of plant protection products is required to maintain their effectiveness and limit the emergence and transmission of AMR microorganisms from horticultural sources.

Biocide and disinfectant use driving antimicrobial resistance

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Biocides are chemicals with antimicrobial properties that are used as antiseptics, disinfectants or preservatives in healthcare, industry and consumer products. They play an essential role in limiting the spread of infectious diseases. The food industry is dependent on these chemicals, and their increasing use is a matter for concern due to their potential to promote emergence of resistant microbial strains. Specifically, the emergence of bacteria demonstrating increased tolerance to biocides, coupled with the potential for the development of a phenotype of cross-resistance to clinically important antimicrobial compounds is of public health relevance.

The aim of this study was to summarize the current state of knowledge on biocide use as a driver of antimicrobial resistance and to identify knowledge gaps.

The role of biocides as selectors of resistant strains, or as inducers of mechanisms involved in antimicrobial resistance has been described in numerous genetic and bacteriological experiments. Studies reporting cross-resistance in clinically important antibiotics are conflicting. However, data establishing risks in the food processing environment as well as data linking the cross-resistance with antibiotics in clinical and food isolates is lacking. Upon the synthesis of the available evidence, prudent use of biocides might be recommended in order to maintain their effectiveness and to limit release in the environment. However, additional research including epidemiologic investigation and analysis of the data from commercial settings is required to better assess the implications of biocide resistance in possible monitoring recommendations for food industry.

Understanding antibiotic prescribing practices: a comparative study of doctors, dentists and veterinarians

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Antibiotic resistance (AbR) is a threat to human and animal health. Contributing factors are diverse, as are stakeholders. A One Health approach is advocated to address the AbR crisis (http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/), and a key strategy is to improve antibiotic prescribing practices. To achieve this, prescribing attitudes and perceptions need to be understood. A comparison of doctors, dentists and veterinarians – the only prescribers of antibiotics in the Australian context – can provide critical information for the design and adoption of policies to improve prescribing practices. This study was undertaken to collect such data.

A survey of doctors, dentists and veterinarians practicing in primary, secondary or tertiary care in Australia was conducted online. A sampling frame was created by integrating a range of professional lists. Demographic information was collected. Questions – generally using a Likert scale – sought information on prescribers' knowledge, attitudes and perceptions of AbR. Significant ($P<0.05$) differences in responses between prescriber groups were identified using Kruskal-Wallis tests.

A total of 547 doctors, 380 dentists and 403 veterinarians completed the survey. Key attitudes and perceptions were noted. Veterinarians were less likely to rate unnecessary use of broad-spectrum agents, prescribing with uncertain benefit, and longer antibiotic courses as "significant", but more likely to rate low doses of antibiotics as "significant" contributors to ABR; dentists, were more likely to rate failure to remove the source of infection as "significant"; and doctors were less likely to consider patients not taking a full course or using leftover antibiotics as "significant".

Doctors and dentists were more likely to perceive antibiotic use in livestock and companion animals as "significant" and "moderate", respectively, whereas veterinarians rated these as making "moderate" and "minimal" contributions to AbR, respectively. Doctors generally rated current levels of antibiotic use in "my principal place of practice" as making a "moderate" contribution to AbR; dentists and veterinarians rated this as "minimal".

Veterinarians generally rated AbR as a "moderate" problem for health of the livestock and food animal industry, but a "minor" problem in other veterinary patients. Doctors and dentists were more likely to rate their own roles as "very important" in preventing or managing AbR.

The majority of respondents across all prescriber groups were aware of the current and increasing problem of AbR, which is an encouraging foundation towards achieving a One Health approach. However, characterisations of AbR more as a human health problem than an animal health problem, and externalisation of responsibility of AbR on to others (by all prescriber groups), represents a challenge to achieving a One Health approach, as individuals may be less critical of their own actions in relation to others.

Exploring pet ownership as a risk factor for extended spectrum β-lactamase (ESBL) infection in humans

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Companion animals often live within homes and share living space with people. In New Zealand, 60% of households have a pet, with 44% having at least one cat and 28% having at least one dog. As multidrug resistant infections become more common in the community, especially those involving extended spectrum beta-lactamase- (ESBL) producing *E. coli*, the role that companion animals play in these human community-acquired infections warrants investigation.

A prospective case-control study was conducted between August 2015 and September 2017. Cases were defined as people with community-acquired urinary tract infection (UTI) caused by newly acquired ESBL- or AmpC beta-lactamase- (AMPCBL) producing Enterobacteriaceae. Both cases and controls were recruited from the Auckland and Northland regions of New Zealand, with randomised dialling selection of controls. A telephone questionnaire was administered to 141 cases and 525 controls. Putative risk factors were assessed using regression analyses and included pet ownership and any other animal contact. Faecal samples from both people and companion animals were submitted from 27 case households. The whole genomes of ESBL- or AMPCBL-producing isolates collected from urine and faecal samples were sequenced and analysed through a bioinformatics pipeline.

In both univariate and multivariate regression, pet ownership did not constitute a risk for human ESBL- or AMPCBL-producing Enterobacteriaceae UTI. Of the 27 case households where at least one pet was sampled, three case households had a dog carrying ESBL-producing *E. coli*. The isolates recovered from the dogs in two of these households were the same MLST-type (ST-131 and ST-38) as those cultured from people in the home, and clustered with those human isolates on whole-genome MLST.

The results of this study suggest that companion animals do not constitute a risk for acquisition of ESBL- or AMPCBL- producing Enterobacteriaceae urinary tract infection in the community. However, animals living with people who carry ESBL-producing *E. coli* may also be carriers; in these cases, pets may play a role in community transmission of ESBL *E. coli*.

Bayesian latent hierarchical model for detecting MIC creep

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Public health officials seek to properly interpret the volumes of data generated by surveillance programs such as the US National Antimicrobial Resistance Monitoring Scheme (NARMS), there is a critical need to develop new/alternative approaches to the statistical analysis of antimicrobial resistance (AMR) data that will detect development of resistance in a timely manner and enable the quick implementation of mitigation measures. AMR data are collected through surveillance programs and describe the concentration of an antibiotic at which an organism ceases to grow and proliferate i.e. a minimum inhibitory concentration (MIC). For statistical analysis, proportion of bacteria in the resistant category is used as an indicator of changes in resistance. The central hypothesis of our project is that statistical analysis based on MIC breakpoints, while simple to conduct, does not facilitate timely detection of changes in resistance. The major issue with statistical analysis based on proportion in the breakpoint categories, is that the average MIC can be increasing long before changes in the proportion above the threshold are statistically detectable i.e. MIC creep. The objective with the project was to develop the statistical methods that facilitate timely detection of MIC creep. We developed a statistical model to detect MIC creep and test the hypothesis that the number of years required to detect MIC creep using a Bayesian latent class hierarchical model is less than an analysis based on the MIC breakpoint-based categories analysis. For this project we demonstrated the method using NARMS human data for Salmonella. We found that MIC values for non-resistant category were statistically significant increasing from 1996 to 2014 for Typhimurium serotype tested on chloramphenicol antibiotic, while no significance was detected on the proportion of non-resistant category. Also our proposed pair-wise comparison for MIC values between consecutive years could mimic the observed MIC trend reasonably well. This analysis enables more timely detection of emerging resistance. The impact will be, that public health officials can implement targeted antimicrobial stewardship programs sooner.

Design of dosage regimens that least select for resistance

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Optimisation of antimicrobial treatment is a cornerstone in the fight against antimicrobial resistance. Various national and international authorities and professional veterinary and farming associations have released generic guidelines on prudent antimicrobial use in animals. However, these generic guidelines need to be translated into a set of animal species- and disease-specific practice recommendations. This presentation focuses on prevention of antimicrobial resistance and its complex relationship with treatment efficacy, highlighting key situations where the current antimicrobial drug products, treatment recommendations, and practices may be insufficient to minimize antimicrobial selection. The topic requires a multidisciplinary approach, involving microbiology, pharmacology, clinical medicine, and animal husbandry. Four key targets for implementing the concept of optimal antimicrobial treatment in veterinary practice need to be considered: (i) reduction of overall antimicrobial consumption, (ii) improved use of diagnostic testing, (iii) prudent use of second-line, critically important antimicrobials, and (iv) optimisation of dosage regimens. Important examples of practice recommendations for achieving these four targets will be selected from specific conditions that account for most antimicrobial use in pigs (intestinal and respiratory disease), cattle (respiratory disease and mastitis), dogs and cats (skin, intestinal, genitourinary, and respiratory disease), and horses (upper respiratory disease, neonatal foal care, and surgical infections). Finally, the importance of education and research needs for improving antimicrobial use in the future, including key elements of precision medicine, will be highlighted.

Guardabassi L, Apley M, Olsen JE, Toutain P-L, Weese JS. 2018. Optimization of Antimicrobial Treatment to Minimize Resistance Selection. *Microbiology Spectrum* **Article in Press**.

Antimicrobial resistance (AMR): the New Zealand perspective

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When measured in terms of antimicrobial use per kilogram of biomass, New Zealand is considered to be a relatively low user in livestock production but a relatively high user in human medicine. Although there are limited data on antimicrobial resistance (AMR) in animals in New Zealand, evidence indicates AMR in animals is generally low compared to other countries. However, the recent emergence of a resistant strain of *Campylobacter jejuni* associated with the poultry supply in North Island showed how rapidly this situation can change. This underlines the need to continue to reduce unnecessary use of antimicrobial use in humans and animals and seek alternative ways of preventing infection without compromising health and welfare.

In this talk I will report the results of recent estimates of antimicrobial use in animals and people in New Zealand, compared to other countries, and provide examples of ongoing research using genome sequencing and modelling to explore the zoonotic transmission of AMR pathogens between animals (livestock and companion animals) and people. I will also address the question: what will happen to AMR in humans if we successfully reduce antimicrobial use in animals?

Antimicrobial resistance (AMR): the Australian perspective

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Antimicrobial resistance (AMR) is a global issue of increasing importance. Australia's engagement with the issue of AMR has been broad and spans both human and animal populations, industries and governing bodies. Indeed, the government's approach to the issue could be considered the first example of a cross-disciplinary One Health response to an issue that spans species in Australia.

Australia's history with respect to AMR is chequered. An early proactive approach, taken in the late 1990's with a report tabled by the Joint Expert Technical Advisory Committee on Antimicrobial Resistance (JETACAR) made strong recommendations for oversight and intervention, but this was followed by 13 years of almost complete inaction. However, the development of the Antimicrobial Resistance Standing Committee (AMRSC) in 2012 with the aim of oversight of AMR in Australia and the Australian Antimicrobial Resistance Prevention and Containment (AMRPC) Steering Group, chaired jointly by the Commonwealth Chief Veterinary and Medical Officers, signalled the start of a structured cross-disciplinary response. Reports were commissioned and tabled on surveillance and reporting of antimicrobial resistance and usage for human health (2013) and animal health (2014) and in 2015 a national AMR strategy (2015 – 2019) was released and an implementation plan followed in 2016.

In addition, and likely as a response, to these initiatives at the level of government, in recent years many other stakeholders in Australia have moved forward in this space. There is now increased engagement of state government, industry, peak and regulatory bodies in the area of AMR. Each of these stakeholders are engaged in differing (and often multiple) strategies to address AMR, inclusive but not limited to: collection of surveillance data, development of consistent testing and reporting strategies, publication of biosecurity, infection prevention and prescribing guidelines, and development of teaching material. Numerous research streams have been developed within a One Health framework and are gaining funding across a number of disciplinary areas, where previously they may not have been looked upon favourably. Furthermore and, in my opinion, most excitingly, it is obvious that the defensive attitudes that may have played a role in limiting progression in the early 2000's are now rarely encountered across any stakeholder or contributor within this space. This marked cultural shift signals the potential for continuation and enhancement of the collegiate and beneficial collaborative processes that have been seen in recent years, paving the way for value adding within the One Health framework.

While Australia still has a long way to go before we can be fully comfortable with our knowledge and response surrounding AMR, we certainly appear to be moving, at speed, in the right direction.
