ANTIMICROBIAL RESISTANCE AND RAW MEAT DIETS FOR PETS: AN EMERGING CONCERN

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INTRODUCTION

Raw meat diets remain an important alternative diet choice for many pet owners. Proponents of raw feeding suggest that this diet option is highly beneficial, is more 'natural', and has many health benefits for the pet. However, raw meat diets for pets have been demonstrated to be contaminated with bacteria with zoonotic and pathogenic potential, including *E. coli*, *Salmonella* spp., *Campylobacter* spp. and *Listeria* spp., among others. Furthermore, there is increasing concern surrounding the growing evidence that raw meat diets may harbour antimicrobial-resistant (AMR) bacteria. Pets and their owners often share a very close relationship and frequently share similar microbiomes. Therefore, there is risk for transmission of AMR-bacteria between them.

WHAT IS ANTIMICROBIAL RESISTANCE (AMR) AND WHY IS IT A CONCERN?

AMR is defined by the World Health Organisation as "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".

Although penicillin was discovered in 1928, it was not available for mass therapeutic use until the mid-1940s. The 'Golden Age' of antibiotic discovery was underway by the 1950s, and many classes of antibiotics still used today were discovered in the period up to the late 1960s. Antibiotics were so successful in treating bacterial infections that in the 1970s, it was believed that bacterial infectious disease was largely controlled, and research resources were diverted. In the following decades, few new classes of antibiotics were discovered (Figure 1).

Unfortunately, intense selection pressure on bacteria due to mass production of antibiotics, easy antibiotic availability and indiscriminate and inappropriate antibiotic use in humans and animals resulted in the evolution and global dissemination of a range of antimicrobial resistance mechanisms. In the 1990s and early 2000s, AMR-infections increased dramatically, becoming one of the most significant threats to human health, and in 2011, the director of the World Health Organisation warned that, without urgent action, the world would enter a 'post-antibiotic era', in which many common infections would no longer be treatable.

Antibiotic classes which are authorized for use in humans and animals are categorised by the World Health Organisation as 'important, 'highly important' and 'critically important', and 'highest priority critically important'. Examples of highest priority critically important antibiotic classes include the quinolones, 3rd and 4th generation cephalosporins and polymyxins. Additionally, some classes of antibiotics, such as carbapenems, are only authorised for human use.

AMR presents an enormous human and animal health, welfare and economic burden globally. The UK 2016 Review on Antimicrobial Resistance predicted 10 million deaths worldwide by 2050 due to antimicrobial resistance[1], while another study suggested that in 2019, 1.27 million deaths globally were attributable to AMR[2]. There is increasing resistance to highest priority critically important antibiotics, and many resistant bacteria are zoonotic.

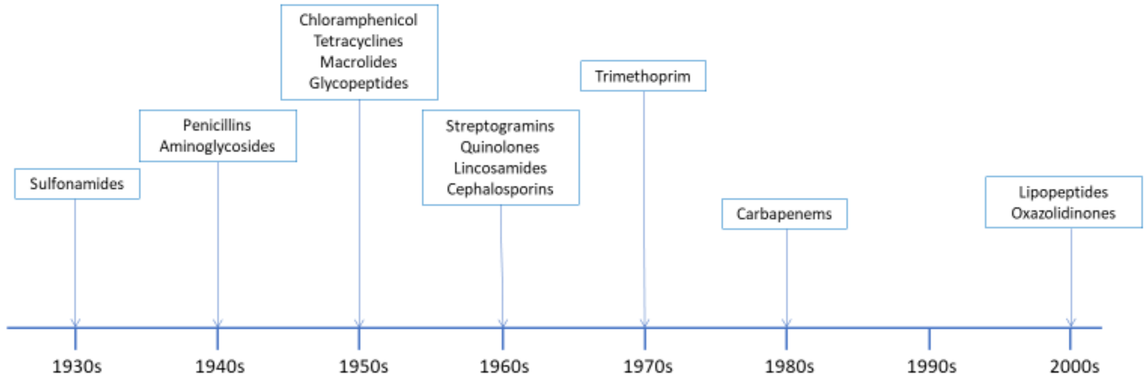

Figure 1: Timeline of development of new antibiotic classes in the 20th and 21st Centuries

KEY ANTIMICROBIAL RESISTANCE MECHANISMS

Broadly speaking, bacterial AMR can be classed as:

- Naturally occurring (intrinsic) resistance: Resistance occurs universally within a species of bacteria, independent of antibiotic exposure and not related to horizontal gene transfer.
- Induced (acquired) resistance: Bacteria acquire AMR genes via horizontal transfer of mobile genetic elements such as plasmids.

If bacteria are resistant to more than one antibiotic class, they may be defined as[3]:

- Multidrug resistant: acquired non-susceptibility to at least three antimicrobial classes
- Extensively drug resistant: susceptible to only one or two antimicrobial classes
- Pan drug resistant: non-susceptibility to all antimicrobial classes

There are some key AMR mechanisms of concern. One such mechanism is extended-spectrum beta lactamase production, observed in many bacteria important in human and veterinary medicine, including the *Enterobacteriaceae* (e.g. *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp., *Proteus* spp.), as well as *Pseudomonas* spp. and *Acinetobacter* spp. Extended-spectrum beta-lactamases confer resistance to penicillins, cephalosporins (including 3rd and 4th generation cephalosporins) and monobactams (aztreonam). The genes encoding extended-spectrum beta-lactamases are commonly carried on plasmids, therefore are transmissible, and are frequently associated with co-carriage of genes mediating resistance to other highest-priority critically important antibiotics. Therefore, extended-spectrum beta-lactamase producing bacteria are often multidrug resistant.

ANTIMICROBIAL RESISTANCE AND RAW DIETS: CURRENT EVIDENCE

There is a developing body of evidence which has identified raw meat diets for pets as being contaminated with AMR-bacteria. Therefore, these diets may pose a risk of AMR-bacteria transmission to animals and humans exposed to them.

Raw meat diets

Globally, samples of raw meat diets for dogs and cats have been found to be contaminated with AMR-*Enterobacteriaceae,* including *E. coli*, *Salmonella* and *Enterobacter* spp., which have zoonotic potential[4–10]. Importantly, the vast majority of the diets tested in these studies were supplied frozen, a process which is widely believed to mitigate the risk of harmful bacteria within the products.

In the UK, a study of 110 commercially available, preprepared frozen raw meat diet and 23 cooked kibble diet samples identified that AMR-*E. coli* was present in nearly 40% of raw samples tested[11]. Extended-spectrum beta-lactamase producing *E. coli,* and third generation cephalosporin resistant *E. coli*, was isolated from 14% and 16% of raw samples, respectively. AMR-*Salmonella enterica* was isolated from 2 raw meat diet samples. No *Enterobacteriaceae* were isolated from any of the cooked kibble samples. Notably, whole genome sequencing identified important acquired plasmid-borne AMR-genes within the *Enterobacteriaceae* isolates, demonstrating the potential for transmission of AMR.

Pets fed raw meat diets

Alongside the research into the risks of raw meat diets themselves, there are concerns that pets fed a raw diet may also become a risk for AMR-bacteria carriage and transmission.

Studies have demonstrated that provision of a raw meat diet is a risk factor for the shedding of AMR-bacteria by dogs and cats[12–15].

In a study from the UK of 432 healthy dogs (239 non-raw fed, 193 raw fed), dogs fed a raw diet were significantly more likely to shed extended-spectrum beta-lactamase producing *E. coli*, third-generation cephalosporin-resistant *E. coli*, and multidrug-resistant *E. coli* than dogs fed a cooked diet. In fact, the most significant risk factor for shedding of AMR-*E. coli* was feeding a raw diet; over and above other risk factors such as visiting a veterinary clinic or provision of antibiotics in the preceding three months. In that study, 40% of raw fed dogs shed AMR-*E. coli*, approximately 25% shed extended-spectrum beta-lactamase producing *E. coli*, and 33% shed third-generation cephalosporin-resistant *E. coli*, compared to 14%,2% and 5% of dogs fed a cooked diet, respectively. Importantly, as with the raw meat diets themselves, whole genome sequencing identified important transmissible AMR-genes within the *E. coli* isolates.

A study from Brazil analysed the presence of AMR-*E. coli* in the faeces of dogs fed raw meat diets or conventional cooked diets. This study found that *E. coli* isolates from raw fed dogs were frequently multidrug resistant, and carried genes conferring resistance to highest-priority critically important antibiotics[16].

A cohort study of healthy cats from the Netherlands identified further concerning results; extended-spectrum beta-lactamase producing *Enterobacteriaceae* were isolated from 89% of faecal samples collected from raw fed cats over three weeks, compared to 6% of samples from non-raw fed cats, and a significant association was found between shedding of extended-spectrum beta-lactamase producing bacteria and feeding a raw meat diet[5].

Dogs fed raw meat diets have also been implicated in the transmission of AMR-*Salmonella* spp. to people. An investigation into an outbreak of Salmonellosis in people in Canada identified that dogs fed a raw meat diet were a major source of infection[17]. Half of the affected people were infants, highlighting the particular risk to vulnerable individuals in society.

TRANSMISSION RISKS

There may be many potential AMR-bacteria transmission routes resulting from the provision of contaminated raw meat diets, both direct and indirect, which could pose a risk to animals, humans and the environment:

- Direct contact: Contact with the food itself, or via close contact with the raw-fed pet (for example, through licking hands and faces) could pose a risk of transmission to in-contact people and animals. Co-carriage of AMR-*Enterobacteriaceae* by dogs and owners in the same household has been demonstrated[18], therefore if raw-fed pets are at greater risk of shedding AMR-bacteria, there could be increased risk of transmission and co-carriage within the home.
- Indirect contact: This may be important within the home (for example, contamination of shared food areas such as the fridge or preparation spaces in the kitchen, shared utensils, or from handling contaminated items utilised by the raw-fed pet such as toys and soft furnishings). Studies have shown that pet owners may practice varied, inconsistent or inadequate practices surrounding pet food hygiene and that messaging surrounding appropriate measures may be confused or not be reaching the desired audience[19–21]. Furthermore, raw meat diet packaging may also pose a risk-one study demonstrated frequent packaging faults and leakage of contaminated material following product defrosting[11].

Risks within the veterinary clinical environment

Veterinary professionals have close and frequent contact with multiple patients each day. Therefore, they may be at higher risk of contracting bacteria from patients and contaminated environments such as kennels and bedding. Indeed, veterinary professionals have been identified previously as a high-risk population for faecal carriage of AMR-*E. coli*[22]. Contamination of clinical environments with AMR-bacteria, and transmission of AMR-bacteria between veterinary patients and the veterinary hospital has been demonstrated[23]. Therefore, raw fed patients shedding AMR-bacteria to a greater extent may indeed pose a greater risk to the clinical environment. Bacterial shedding by raw-fed patients may pose a hazard for other at-risk veterinary patients, such as the elderly, the very young, patients undergoing surgery and those undergoing treatment with immunosuppressive medication such as those with autoimmune disease, or chemotherapy. This risk may occur because of direct contact, contamination of the hospital environment, or via patient-to-patient spread by veterinary professionals dealing with multiple patients. There are currently no official guidelines as to how to manage raw fed patients within the clinical environment, although policies such as barrier nursing and/or isolation of such patients are employed in some practices. Further research is required to determine the risks of transmission of AMR-bacteria from raw meat diets, and the pets fed them, within the home and clinical environments.

EMERGING CONCERNS

As well as the documented AMR risks associated with *E. coli* and *Salmonella* spp. from both raw meat diets and the pets fed them, there are emerging concerns surrounding other bacteria of concern in human and veterinary medicine. Studies have demonstrated the presence of the so-called ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, *Enterobacter* spp) in samples of raw meat diets. These bacteria are of serious concern in human medicine, particularly in hospital-acquired infections, and infections of immunocompromised patients such as those with cystic fibrosis. They have a propensity to be highly antimicrobial-resistant, including to many highest priority critically important antibiotics. Furthermore, they are an emerging concern in veterinary medicine; they were the most prevalent gram-negative bacteria isolated from veterinary hospitals in a recent study[24]. They have also been implicated in disease in veterinary patients, with multidrug-resistant infections caused by *Acinetobacter* spp., *Pseudomonas* spp., and *Enterobacter* spp. being reported in dogs, cats and horses[25–27].

A study from the USA identified multidrug-resistant *Enterobacter cloacae* and *Klebsiella pneumoniae* in raw meat diets[9]. Furthermore, research from the UK has identified *Acinetobacter baumanii* complex, *Pseudomonas* spp., and *Enterobacter* spp., carrying important AMR genes, within samples of commercially available frozen raw diets[28].

CONCLUSIONS

There is a growing body of evidence surrounding the AMR risks associated with raw meat diets, and the pets fed them. Due to the potential risks to humans, animals and the environment, raw meat diets could be considered a truly 'One Health' concern. AMR is a global problem, and without intervention, the situation will only deteriorate. As veterinary professionals, we must be mindful of both our animal health and public health obligations, and continue to educate and engage with pet owners and other professionals regarding the potential risks associated with raw meat diets.

Word count: 1954

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