

Editorial: Symposium on Antimicrobial Resistance in Bacteria from Animals

In December 2007, the Editorial Board of *Animal Health Research Reviews* decided that the journal should organize a symposium on antimicrobial resistance in bacteria from animals. This topic was chosen although antimicrobial resistance has been the subject of several conferences over the recent past. It was agreed that the symposium would seek to be forward-looking and to emphasize research on procedures, methods and approaches that may be used to reduce the use of antimicrobials in agriculture and in companion animals. In earlier days, discussions of antimicrobial resistance tended to be more confrontational, with opposing camps for and against the use of antimicrobials in agriculture. There was also a tendency to consider only the human health consequences and not the animal health implications of an increasingly resistant population of pathogenic and reservoir bacteria. The articles in this symposium show that we have moved beyond that and we are concentrating on new strategies and research to reduce the use of antimicrobials in food animals, companion animals and humans. There is a clear recognition of the need to develop a better understanding of factors other than drug use that also influence the development and survival of drug-resistant bacteria.

I am grateful to the authors who put considerable effort into producing manuscripts that are insightful, informative and easy to read. The authors are all established researchers with busy schedules who were willing to devote time to share their expertise and ideas with our readers. I am also very appreciative of the contributions of the many reviewers who provided critical commentary, often within a very restricted time frame. Their advice led to improvements of the manuscripts.

The series of articles that constitute the symposium is arranged in two sections. The first section consists of critical in-depth reviews that present the current state of knowledge of antimicrobial resistance in bacteria associated with production agriculture and companion animals. The reviews are focused on assessment of published research, identification of gaps in knowledge, areas of controversy, significant trends, and areas that need further investigation. The literature is substantial and there is no shortage of controversy; no one was able to keep within the page limits that were established. The second section consists of longer reviews that highlight the present state of development of alternatives intended to reduce the consequences of using antimicrobials

in agriculture and in companion animals. The reviews emphasize the strengths and limitations of each approach.

The authors have done an outstanding job of reviewing the literature and providing astute and insightful commentary. The first section begins with a thoughtful discussion of aspects of antimicrobial resistance and transmission that are important for understanding the threats posed by bacterial adaptations to an antimicrobial world. Boerlin and Reid-Smith highlight the potential of recent understanding of the concepts of the mutator state, mutant selection window, and mutant prevention concentration in contributing to strategies for slowing the development of antimicrobial resistance. Mutation, various transmissible genetic elements, selection, and clonal and horizontal transfer are all discussed in relation to their roles in the development and transfer of antimicrobial resistance. These authors stress the importance of a better understanding of the epidemiology of not only the microorganisms but also the genes and transferable elements themselves, which may involve nonpathogenic bacterial reservoirs in locations such as the intestine. Their 'confusogram' is an elegant depiction of the complexity of the connections among the various microbial, animal and environmental factors.

Prescott delivers a strong message on the need to develop and implement strategies for antimicrobial use in animals that will lead to reduced use. He argues effectively that antimicrobial stewardship is a critical component of several steps needed to ensure that we do not slide into a post-antibiotic era. Aarestrup and colleagues present comprehensive data from 18 countries to demonstrate that antimicrobial resistance is creating a problem for the selection of antimicrobials for therapy of bacterial diseases in pigs. They note that variability in the susceptibility patterns for many swine pathogens requires that local data be used to guide initial therapy until antimicrobial susceptibility test results are obtained. The authors propose that good management practices be used to minimize dependence on antimicrobials in swine production.

Gyles, in a pinch-hitting role, reviews antimicrobial resistance in avian pathogenic *Escherichia coli* (APEC), commensal *E. coli*, *Salmonella* and *Campylobacter*. He notes that the data from various countries are highly variable, with a tendency for low frequencies in the Scandinavian countries, moderate frequencies in the USA

and Canada and high frequencies in China. Areas of concern that are highlighted include the high frequency of resistance of APEC to a wide range of antimicrobials, transmissible plasmids that encode resistance to extended spectrum beta-lactams and other antimicrobials, and the ability of *Campylobacter* to rapidly develop resistance to fluoroquinolones. Call and colleagues succeed in succinctly capturing the complexity of the dynamics of antimicrobial resistance in bacteria from cattle. They provide a convincing argument to show that linkage of antimicrobial resistance genes to fitness traits can be a major determinant of persistence of resistant bacteria in cattle populations. They give hope that identification of host and management factors that select for these traits may lead to new avenues for the control of drug-resistant bacteria in cattle.

Weese addresses a neglected area – antimicrobial resistance in companion animals. He uses staphylococci, streptococci, enterococci, *E. coli*, *Salmonella*, *Pseudomonas* and *Acinetobacter* to discuss issues of importance to both pet health and human health. He raises the problem of methicillin-resistant *Staphylococcus pseudintermedius*, which may become important in the health of dogs, and the possibility that uropathogenic *E. coli* may be transferred from pets to people. He points out that vancomycin-resistant enterococci (VRE) are uncommon in animals but multi-drug resistant enterococci are, and that enterococci that are resistant to most antimicrobials, except vancomycin, are sometimes encountered in clinical specimens. Wassenaar and Silley paint a clear picture of the relationship between antimicrobial resistance in bacteria from animals and antimicrobial resistance in human pathogens. They argue convincingly that the situation is complex and the resistance pattern observed in a bacterial population is not necessarily a reflection of antimicrobial use. Although they address the matter by use of different examples, the argument is reminiscent of those advanced by Call and colleagues. Wassenaar and Silley present data to show that the major problems of drug resistance in human pathogens are associated with antimicrobial use in humans, rather than in animals. They advocate measures to reduce the use of antimicrobials and to intensify the efforts to discover new types of antimicrobials.

The second part of the symposium begins with a paper by Potter and coworkers on the use of vaccines in animals as a means of reducing dependence on antimicrobials. These authors indicate that vaccination has proved to be a highly efficient disease control measure but success has been limited to a number of acute diseases. Developments in genetic manipulation, genomics, identification of *in-vivo* expressed antigens, rational and controlled attenuation of microorganisms, DNA vaccines, and live vectored vaccines are beginning to break down the barriers to more extensive use of vaccines against animal and human diseases. The considerable attention that is being paid to vaccines that promote mucosal immunity

and/or cellular immunity and development of novel adjuvants and immunomodulators offer considerable promise for a bright future for vaccines as alternatives to antimicrobials. Callaway and colleagues write on the use of competitive exclusion (CE) cultures, probiotics and prebiotics for pathogen reduction. They observe that results of studies of effectiveness vary considerably, possibly because of the marked variations in the poorly characterized intestinal flora of animals and that one of the difficulties in the application of CE cultures and probiotics is that the live organism preparations are susceptible to destruction by antimicrobials in feeds. Some products are in wide use against *E. coli* O157:H7 and against *Salmonella*. Claims for these products extend beyond protection against pathogens and several products claim to increase growth rates, increase milk yield and/or increase meat production.

Johnson and colleagues discuss the promise and the limitations of bacteriophages for prophylaxis and therapy of diseases of poultry, pigs and cattle. Phages have been very effective against experimental *E. coli* and *Salmonella* infections in pigs, poultry and calves, and against *Campylobacter* in chickens. However, many aspects of the application of phages under field conditions and the regulatory approval process for phages have yet to be explored. Sang and Blecha tackle the subject of antimicrobial peptides (AMPs) and bacteriocins as alternatives to antibiotics. These researchers identify various classes of AMPs that originate with bacteria, fungi, plants, insects, amphibians, Arachnida, animals and humans. They identify the spectra of antimicrobial activities for various classes of AMPs, including bacteriocins, and note that many target bacterial membranes, are active at nanomolar concentrations, and may have immunoregulatory functions. Natural or modified AMPs are at various stages: preclinical, clinical trials, or in use.

Fittingly, the final article is devoted to novel approaches to the discovery of antibacterial agents. Taylor and Wright document the poor rate of discovery of new antibiotic chemical classes over the past 35 years and identify novel approaches to the discovery of new agents as well as roadblocks to discovery. A major difficulty in screening by traditional methods is differentiating 'new' antibiotics from those discovered previously. The authors identify several new approaches based on novel ideas and recent developments. Approaches that seem worthwhile include revisiting antibiotics that were discarded, use of high-throughput small molecule separation and analysis technology to identify new compounds, identifying new biosynthetic gene clusters in sequences of genomes or metagenomic libraries from environmental sources, exploration of non-traditional targets such as siderophore or LPS biosynthetic pathways or efflux pumps, structural modifications of known antimicrobial chemical scaffolds, and development of synthetic antibacterial agents.

The 12 articles represent an impressive recap of the state of antimicrobial resistance in bacteria from animals and thoughtful discussion of approaches that may be taken to address the problem. There is complete agreement that the problem is severe and complex: antimicrobial use selects for resistance, but many other factors

contribute to the evolution of drug-resistant bacteria and their persistence.

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