

## Antibiotics and the search for alternatives: pursuit and paradox

**Harvey M. Scott**<sup>1,2</sup>, Raghavendra G. Amachawadi<sup>2</sup>, Patrick Boerlin<sup>3</sup>, James S. Drouillard<sup>4</sup>, Tiruvoor G. Nagaraja<sup>2</sup>, Michael D. Tokach<sup>4</sup>.

<sup>1</sup>Department of Veterinary Pathobiology, Texas A&M University, College Station, TX, USA.

<sup>2</sup>Department of Diagnostic Medicine/Pathobiology, Kansas State University, Manhattan, KS, USA.

<sup>3</sup>Department of Pathobiology, University of Guelph, Guelph, ON, Canada.

<sup>4</sup>Department of Animal Sciences & Industry, Kansas State University, Manhattan, KS, USA.

The quest for viable alternatives to antibiotics in animal agriculture stretches back decades, with search intensity tied closely to levels of concern about expanding levels of antimicrobial resistance. Attempts to identify effective products have focused largely on replacements for antibiotic label claims relating to growth promotion and prevention. Timely introduction of products to the market can be more readily achieved under the status of “Generally Regarded as Safe” (GRAS), which has led to a proliferation of naturally derived plant products (e.g., essential oils), or else expanded dosing of common nutrients (e.g., metals). Several case studies from Europe and North America will be presented, including of zinc supplemented at extremely high levels (2,000 - 3,000 ppm of feed) for short periods in the post-weaned pig, of copper supplemented at higher than recommended nutrient levels in both monogastrics and ruminants, and of oregano oil and menthol (two essential oils) being fed to multiple food animal species. Readily explained co-selection for antibiotic resistance abounds; for example, Zn selects for *Staphylococcus aureus* strains bearing the *czrC* gene – often linked to the *mecA* gene encoding resistance to methicillin on the SCC*mec* cassette. The rise and spread of livestock-associated MRSA (LA-MRSA) in northern Europe during the past 20 years maps closely to the introduction of high doses Zn. Similarly, the plasmid-borne *tcrB* gene has been shown to select for strains of *Enterococcus* spp. that are highly resistant to copper, as well as tetracyclines (*tet*(M)), macrolides (*erm*(B)) and vancomycin (*vanA* – Europe only). Paradoxically, while metal resistance (and the potential for co-selection) in Gram positive bacteria is well-characterized, the same is not true for Gram negatives such as *E. coli* and *Salmonella* where paradoxes abound and the response of bacterial populations to *in vivo* selection pressures is far from clear. Similarly, though measurable effects on resistance levels among gut bacteria may exist, the differential effect of these products on Enterobacteriaceae is likely of greater importance than their role in selecting for resistance.