

# Food Safety Symposium: Potential Impact of Reduced Antibiotic Use and the Roles of Prebiotics, Probiotics, and Other Alternatives in Antibiotic-Free Broiler Production

## Historic perspective: Prebiotics, probiotics, and other alternatives to antibiotics<sup>1,2</sup>

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**ABSTRACT** Applications of antimicrobials in food production and human health have found favor throughout human history. Antibiotic applications in agricultural and human medical arenas have resulted in tremendous increases in food animal production and historically unprecedented gains in human health protection. Successes attributed to widespread antibiotic use have been accompanied by the inadvertent emergence of antibiotic-resistant bacteria. A major problem associated with this emerging resistance is the crossover use of some antibiotics in agricultural settings as well as in the prevention and treatment of human disease. This outcome led to calls to restrict the use of human health-related

antibiotics in food animal production. Calls for restricted antibiotic use have heightened existing searches for alternatives to antibiotics that give similar or enhanced production qualities as highly reliable as the antibiotics currently provided to food animals. Agricultural and scientific advances, mainly within the last 100 yr, have given us insights into sources, structures, and actions of materials that have found widespread application in our modern world. The purpose of this presentation is to provide a historic perspective on the search for what are generally known as antibiotics and alternative antimicrobials, probiotics, prebiotics, bacteriophages, bacteriocins, and phytotherapeutics.

**Key words:** probiotic, prebiotic, bacteriophage, bacteriocin, essential oil

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## INTRODUCTION

Selman A. Waksman is credited with developing the term antibiotics in 1942, whereas his graduate student, Albert Schatz, is credited with discovering the antibiotic streptomycin (Waksman, 1941; Waksman and Schatz, 1943). Questions regarding the use of bactericidal or bacteriostatic agents in experimental animals to alter intestinal flora was pioneered by Black et al. (1942), Nielsen and Elvehjem (1942), and Moore et al. (1946), who recognized growth retardation in laboratory animals given succinylsulfathiazole, sulfasuxidine,

or streptomycin. Adding these drugs to animal feed reduced growth in laboratory animals and induced a decrease in available folic acid. The negative growth effects of these drugs could be countered by making available to the animals increased levels of dietary folic acid. However, by administering sulfasuxidine, streptomycin, and streptomycin to chicks, Moore et al. (1946) sought to induce vitamin and other nutritional deficiencies and to completely inactivate intestinal bacteria, creating an experimentally sterile research animal. Although the drugs failed to create sterile conditions in the intestinal tracts of these animals, sulfasuxidine and streptomycin, given with adequate amounts of dietary folic acid, reversed the negative growth effects produced by administering these drugs alone as well as the negative effects in chicks given only folic acid. Cunha et al. (1949), Stokstad et al. (1949), and Jukes et al. (1950) realized increased growth in pigs and chickens given diets containing dried mycelia from aerobic cultures of *Streptomyces aureofaciens*. The unknown “animal protein factor” produced by *S. aureofaciens* was later identified as aureomycin (chlortetracycline) along with vitamin B<sub>12</sub>. In 1951, antibiotics were approved by the US Food and Drug Administration as animal feed ad-

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ditives without a veterinary prescription. Beginning in the early 1950s, regulations regarding antibiotic supplements for food animals were set by European countries (Castanon, 2007). Coates et al. (1951, 1955, 1963) proposed that antibiotics increase feed efficiency in chickens through direct effects on microflora by reducing subclinical infection and colonization by opportunistic enteropathogens.

### **The Dilemma**

Over the past few decades, increases in the incidence of human infections by antibiotic-resistant bacteria have been documented (Threlfall et al., 2000; Silbergeld et al., 2008). The growing number of incidences of antibiotic resistance has been hypothesized to be directly related to the overuse, and sometimes unwarranted use, of antibiotics required for human medical prophylactics and therapeutics in food animal production. During the last half century, dependence on antibiotics to enhance food animal production has expanded (Hamer, 2002). Concurrently, human medicine has experienced an increased prescription of antibiotics as a precaution against primary and secondary infection and, in bacterial therapeutics, at times an inappropriate prescription of antibiotics against viral infection. Overdependence on and at times abuses of agricultural and medical antibiotics have inadvertently converged in a minor crisis event, resulting in the ban of agricultural uses of antibiotics that are also used to control infections in humans (Heuer et al., 2002; Soulsby, 2007; Huyghebaert et al., 2011).

Controversy continues over the responsibility for the real and dramatic increase in antibiotic resistance among human pathogens. Food animal producers see human medical practitioners and their patients as the focus of the problem and cite misdiagnosis, patient psychological satisfaction, and patient misuse as central to the problem of increased antibiotic resistance. Medical practitioners cite, among a variety of reasons, widespread and prolonged application of subtherapeutic doses of the antibiotics used in human medical practice to food animals and supplementation of food animal diets with antibiotics. The growing controversy and expanding body of convincing scientific data have captured public attention, resulting in calls for increased scientific and medical vigilance, the banning of antibiotic applications in food animal production, and a more judicious use of antibiotics in human prophylactic and therapeutic treatments. The Union of Concerned Scientists estimates that 70% of antibiotics and related drugs used in the United States are used in animals, whereas the Animal Health Institute reports a much lower usage number (Mellon, 2001). Jones and Ricke (2003) suggest that differences in numbers may depend on the sources of those numbers and how the numbers are calculated. Depending on whether surveys are conducted by food animal producers or human health

care agencies, findings of the survey may vary; however, some surveys conducted by reliable sources indicate that similar levels of antibiotics are used in agricultural and human health arenas. The overriding result has been calls to limit or eliminate the use of antibiotics of human importance in food animal production.

### **Old Ideas with New Directions**

**Probiotics: Living Digestive Microbial Stimulants.** Lactic acid bacteria are at the historic core of probiotic health supplements and therapeutics. The more modern concepts of probiotics have their inception in the works of Ilya Mechnikov (also known as Elie Metchnikoff; 1845–1916). In addition to Mechnikov being awarded the Nobel Prize in 1908 for his work on phagocytosis, he may be considered the father of modern probiotics (Fuller, 1992). His studies regarding probiotics were based on the observations of Stamen Grigorov (1878–1945), a Bulgarian microbiologist, who documented the health benefits of Bulgarian yogurt and identified the active organism in this food staple as *Lactobacillus bulgaricus*, today known as *Lactobacillus delbrueckii* ssp. *bulgaricus*. Mechnikov famously promoted the idea that yogurt and its bacterial constituents were essential ingredients contributing to the longevity seen in Bulgarian peasants. However, the production, consumption, and noted health qualities of yogurt were also well known to the peoples of the Middle East and Asia and predate these more modern observations by perhaps 5,000 yr. One influential episode highlighting its therapeutic use relates how Suleiman the Magnificent (1494–1566) sent a physician from his Turkish court to prescribe yogurt and successfully treat the severe diarrhea suffered by Francis I of France (1494–1547). Guarner et al. (2005) attributes the origin of the term “probiotika” to Werner Kollath who, as related by Vergin (1954), proposed the term to designate “active substances that are essential for a healthy development of life.” The Greek meaning of the term is “for life,” as opposed to “antibiotics” (“against life”). Fuller (1992) describes how the word probiotic was first used by Lilly and Stillwell (1965) “to describe substances secreted by one microorganism which stimulates the growth of another.” Parker (1974) used the term probiotic to describe “organisms and substances which contribute to intestinal microbial balance.” To exclude the misleading term “substance,” Fuller (1989) revised the definition to refer to “a live microbial feed supplement which beneficially affects the host animal by improving its microbial balance.” In 1992, Fuller again modified the definition to address “mono- or mixed cultures of living microorganisms which beneficially affect the host by improving the properties of the indigenous microbiota,” to stress that the organisms be viable and to avoid the use of the term “substance.” Hamilton-Miller et al. (2003), in an insightful review of the derivation of the term, observed that the definition of a probiotic is

refined as we gain more experience. He then presented the definition by Reid et al. (2003) as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” However, in 1989, the US Food and Drug Administration, as revealed by Miles and Bootwalla (1991), proclaimed that manufacturers had to use the term “direct-fed microbials” to designate “a source of live (viable) naturally occurring micro-organisms,” including bacteria, fungi, and yeasts. Poultry probiotics, experimental cultures and those in commercial production, have been delivered mainly as bacterial isolates or in cocktails. The “gold standard” for probiotics is the undefined cecal or fecal preparation as presented by Nurmi and Rantala (1973). However, an undefined culture presents the potential for introducing a variety of pathogens into chickens and into the food chain. Additionally, probiotic reliability would likely change with each batch because materials must be obtained from a new source each time an inoculum is prepared. Although direct deposition of the probiotic into the crop is the classic mode for delivering an inoculum to the animal, probiotics may be delivered by oral gavage, by spray, in the feed, and in the water. “Competitive exclusion” is a term coined by Lloyd et al. (1977), and the probiotic effect has been variously called bacterial antagonism, bacterial interference, barrier effect, and colonization resistance. Currently, probiotics are viewed as production enhancers to affect the digestive microflora positively to promote performance and to protect against colonization by harmful bacteria and enteropathogens of human importance. Probiotics are thought to act in the host by a variety of mechanisms, with no one outstanding quality. Among the desirable effects of a bacterial probiotic preparation are the production of short-chain fatty acids, medium-chain fatty acids, bacteriocins, low pH, and low redox potential; competition with potential enteropathogens and harmful bacteria for substrates; competition with potential enteropathogens and harmful bacteria for attachment sites on enterocytes; and stimulation of an immune response. Probiotics and probiotic development and commercialization have been embraced by the poultry production industry and offer utility as part of a pathogen intervention strategy.

**Prebiotics: Nonliving Digestive Microbial Stimulants.** The prebiotic is perhaps a newer scientific concept than the probiotic and generally refers to nondigestible feed ingredients with selective effects on the intestinal microbiota. Oligosaccharides are the main components, and the diverse range of materials may be based on any of the hexose monosaccharides, including glucose, fructose, galactose, and mannose (Durst, 1996), with a polymerization degree of between 2 and 20 monosaccharides. Gibson and Roberfroid (1995) introduced “the concept of prebiotic foodstuffs, which can be added to the diet in order to increase the health-promoting attributes of certain aspects of the resident gut bacteria.” They further defined a prebiotic as “a nondigestible food ingredient that specifically affects

the host by selectively stimulating growth and/or activity of one or a limited number of bacteria in the colon, and thus improves health.” In 2007, Roberfroid again defined a prebiotic as “a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health.” Gibson and Roberfroid (1995) offered several criteria for a food ingredient to qualify as a prebiotic: it had to 1) be neither hydrolyzed nor absorbed in the upper part of the gastrointestinal tract; 2) be a selective substance for one or a limited number of beneficial bacteria commensal to the colon, which are stimulated to grow, are metabolically activated, or both; 3) be able to alter the colonic flora in favor of a healthier composition; and 4) induce luminal or systemic effects that are beneficial to the host health. Apparently, only 2 food additives fully meet the criteria for a true prebiotic, the fructooligosaccharides and inulin (Roberfroid, 2007), whereas galactooligosaccharides, a polymer of enzymatically altered lactose, also meet these qualifications. A report by the Food and Agriculture Organization of the United Nations (2007) addressing the availability of prebiotics for human consumption stated that “there were no industry-wide guidelines governing the usage of the term prebiotic and that the world prebiotic market offered over 400 prebiotic food products with more than 20 companies producing oligosaccharides and fibres to be used as prebiotics.” The Food and Agriculture Organization of the United Nations (2007) report listed commonly offered and used prebiotics, such as inulin, fructooligosaccharides, galactooligosaccharides, soy-oligosaccharides, xylooligosaccharides, pyrodextrins, isomaltooligosaccharides, and lactulose. The new, emerging prebiotic compounds listed were pecticoligosaccharides, lactosucrose, the sugar alcohols, glucooligosaccharides, levans, resistant starch, xylosaccharides, and soy-oligosaccharides, some of which were classified by Gibson and Roberfroid (1995) and Roberfroid (2007) as not meeting the qualifications of a prebiotic. Gibson et al. (2004) and Roberfroid (2007) again qualified the criteria for a prebiotic as 1) resistance to gastric acidity, to hydrolysis by mammalian enzymes, and to gastrointestinal absorption; 2) fermentation by intestinal microflora; and 3) selective stimulation of the growth, activity, or both of those intestinal bacteria that contribute to health and well-being. Roberfroid (2007) insisted that resistance does not mean that the food additive is completely indigestible, but that a significant amount should be available in the large intestine for fermentation.

**Bacteriophages: Viral Transmissible Lytic Agents.** The discovery of bacteriophages is attributed in independent discoveries to Felix d’Herelle and Frederick Twort. In 1910, d’Herelle was accredited with the first documented citing of clear circular spots on agar cultures of a coccobacillus that kills locusts. He encountered a similar phenomenon in 1915 when investigating *Shigella* dysentery in French World War I

soldiers. Twort, like d'Herelle, noted and documented clear areas on bacterial agar cultures. d'Herelle gave his discovery the name "bacteriophage," a devourer of bacteria, whereas Twort called his discovery a "transmissible lytic agent." Their contribution was given the title "Twort-d'Herelle phenomenon." Bacteriophages can infect most bacteria and are readily found in most environments colonized by bacteria. Research on animal and human pathogens continued with varying degrees of success and many failures after the initial discovery of these agents; however, with the advent of penicillin and other antibiotics, anti-infection bacteriophage research waned. Nonetheless, continuing investigations revealed insights into structure and phage-host interactions while laying a foundation for the development of molecular biology techniques (Marks and Sharp, 2000). Commercial bacteriophage preparations were marketed in the 1930s, with often overexaggerated claims, and subsequent interest in bacterial disease therapy became almost nonexistent (Barrow and Soothill, 1997). According to Barrow and Soothill (1997), interest in bacteriophage or phage therapy resurged in the 1980s with the work of Smith and Huggins (1982, 1983) and Smith et al. (1987a,b). Experiments using mice indicated that phage treatment generally outperformed treatment with antibiotics, such as streptomycin, tetracycline, ampicillin, and trimethoprim/sulfafurazole (Smith and Huggins, 1982). Experimenting with delivery methods, Smith and Huggins (1982) and Smith et al. (1987a,b) found that *Escherichia coli* infections could be eliminated by per os inoculum, intramuscular injection of phages, or spraying litter with phages. Meanwhile, Soothill et al. (1988) and Soothill (1994) turned their attention to treating burn patient infections. A desirable trait for successful bacteriophages that can be used as therapeutic agents is that the targeted pathogen does not serve as a reservoir for the phage, thereby reducing the development of resistance in the pathogen (Goode et al., 2003). These authors further assert that bacteriophages are likely unsuitable for use in poultry-rearing facilities against enteropathogens because fecal shedding would rapidly lead to resistance. Continuing with this assertion, Goode et al. (2003) stated that the processing plant is the most likely venue for bacteriophage therapy because carcass treatment is a one-time event and it would be very difficult for the bacteriophage to find its way to the farm and lead to resistance. Poultry and farm animal applications have been developed for *Salmonella* (Ibrahim, 1969a,b; Berchieri et al., 1991; Toro et al., 2005; Andreatti Filho et al., 2007; Johnson et al., 2008; Svetoch et al., 2008; Vandeplass et al., 2010), *Campylobacter* (Atterbury et al., 2003, 2005; Cole et al., 2006; Stern et al., 2006; Johnson et al., 2008; Svetoch et al., 2008), *E. coli* (Huff et al., 2002a,b), and *Clostridium perfringens* (Miller et al., 2010).

**Bacteriocins: Bacteria-Killing Proteins.** Bacteriocins were first discovered in 1925 by André Gratia. *Escherichia coli* was one of Gratia's first research models, and he named this new antimicrobial "colicine" be-

cause of its ability to kill the bacterium. The discovery of colicin (current spelling) occurred during a time of heightened search for a reliable treatment against infectious disease pathogens, especially those afflicting humans. Out of this wide search for antimicrobial agents came the recognition and greater understanding of antibiotics, bacteriophages, and bacteriocins. Bacteriocins, which are proteins that come in a range of sizes, may be heat labile or heat stable, and may be resistant or susceptible to a range of proteolytic enzymes. An earlier perception was that bacteriocins were produced only in gram-positive bacteria (Abee et al., 1995). However, the current view is that almost all gram-positive and gram-negative bacteria produce and use bacteriocins to create a defensive or competitive edge (Riley and Wertz, 2002). A common mode of action of bacteriocins is that they disrupt bacterial membranes, resulting in cell death. Some bacteriocins inhibit cell wall synthesis, lipid bilayer function, spore outgrowth, activation of autolytic enzyme activation; simply bore holes in membranes; or attack cellular DNA, ribosomal RNA, or transfer RNA (Riley and Wertz, 2002; Peschel and Sahl, 2006; Sahl and Bierbaum, 2008; Lin, 2009). According to Klaenhammer (1988), 99% of all bacteria make at least 1 bacteriocin. However, a potential obstacle in the search for bacteriocins against any given enteropathogen is that not all bacteria are reactive to a specific bacteriocin, and there is potential for the development of resistance. These traits may require the screening of a large number of producer candidates before an effective bacteriocin may be identified (Coventry et al., 1997; Svetoch et al., 2005). Screening and application may require a combination of approaches. For example, not all *Salmonella* are susceptible to bacteriocins; however, Vincent et al. (2004) demonstrated that resistant strains may become susceptible by acquiring the relevant membrane receptor. Riley and Wertz (2002) suggested that the relatively narrow killing spectrum of bacteriocins may allow them to be used as "designer drugs" that target specific pathogens. An apparent abundance of bacteriocin producers exist among bacteria and archaea. Based on the findings of Peschel and Sahl (2006) and Sahl and Bierbaum, (2008), Lin (2009) observed, "it seems that bacteria have not developed highly effective methods to resist AMPs' (*natural antimicrobial proteins*) including bacteriocins" (italics inserted). Lin (2009) stated further, "it has been proposed that bacteriocins may have multiple low-affinity targets and cause pleiotropic effects on various bacterial targets. Therefore, it is possible that such low-affinity interactions of bacteriocins with multiple targets are not favorable for the development of bacterial resistance." In 1988, Klaenhammer offered the opinion that the only reason we have not isolated more bacteriocins is that few researchers have looked for them.

**Phytotherapeutics: Plants, Plants Extracts, and Essential Oils.** Plants, plant extracts, and essential oil distillates have long traditions in food preservation as

well as long traditions of appreciation for their medicinal, flavor, and odor qualities (Zaika, 1988). Dorman and Deans (2000) cite early systematic investigations by Martindale (1910) and Hoffman and Evans (1911) to characterize the antiseptic qualities of medicinal and medical plants. Some of the bioactive antimicrobial chemical forms derived from plants include terpenoids, phenolics, glycosides, and alkaloids (Huyghebaert et al., 2011). Ginger, pepper, coriander, bay, oregano, rosemary, sage, thyme, cloves, mustard, cinnamon, garlic, lemon, citrus peel (lime, lemon, orange), and tobacco are a few representatives from a very long list of plant products expressing antibacterial properties. Kim et al. (1995) demonstrated, based on the antibacterial and antifungal findings of Kurita et al. (1979, 1981), the usefulness of 11 essential oil extracts against the potential foodborne pathogens *E. coli*, *E. coli* O157:H7, *Salmonella enterica* serovar Typhimurium, *Listeria monocytogenes*, and *Vibrio vulnificus*. Hammer et al. (1999) demonstrated the efficacies of 52 plant oils and extracts against gram-positive and gram-negative bacteria, with some of the oils being effective against gram-positive organisms only. Dorman and Deans (2000) demonstrated antibacterial activity against 25 different genera of bacteria, including animal and plant pathogens and food poisoning and spoilage bacteria. In a review of essential oils and the effects of secondary plant metabolites in poultry production, Brenes and Roura (2010) discussed the attributes of essential oils, such as enhancing the production of digestive secretions, stimulating blood circulation, exerting antioxidant properties, reducing the levels of pathogenic bacteria, and potentially enhancing the immune status.

In conclusion, alternatives to what are generally known as antibiotics are currently receiving greater attention from the scientific community, food animal producers, consumers of commercial food animal products, and providers of human medicine. The scientific community actively continues to seek out alternatives to traditional antibiotics to identify equal- or superior-performing agents. Producers desire a continued means of enhancing food animal performance and ensuring food safety. Members of the medical community wish to protect the vulnerable inventory of disease-fighting antimicrobials currently available. Alternatives are currently available, and the list continues to grow. The goal is to enhance the knowledge base of alternative antimicrobials currently under investigation and to identify additional materials for potential strategic use in food animal production and the protection of human health.

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