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Control of bacterial diseases

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Abstract: Bacterial diseases in poultry are caused by a vast range of bacteria with typical pathogens being *Salmonella* spp., *Escherichia coli*, *Avibacterium paragallinarum*, *Clostridium perfringens*, *Pasteurellam ultocida*, and *Staphylococcus aureus*. In addition, there are food safety bacterial pathogens to consider – the major ones being *Campylobacter* and *Salmonella* spp. These diseases fail to attract the media attention and the headlines given to prominent viral infections such as avian influenza and exotic Newcastle disease. Nevertheless, bacterial diseases continue to remain a problem – in productions system based in both the developing world as well as the developed world. The aim of this paper is take a fresh look at the challenges that lie ahead in the prevention and control of these diseases.

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Introduction

Antibiotics and Antibiotic resistance

Antibiotic resistance (AR) which is defined as the ability of an organism to resist the killing effects of an antibiotic to which it was normally susceptible **(Madigan et al.,2014)** and it has become an issue of global interest **(Sahoo et al., 2010)** This microbial resistance is not a new phenomenon since all microorganisms have an inherent capacity to resist some antibiotics **(Hugo and Russel1998)** However, the rapid surge in the development and spread of AR is the main cause for concern **(Aarestrup et al., 2008)** In recent years, enough evidence highlighting a link between excessive use of antimicrobial agents and antimicrobial resistance from animals as a contributing factor to the overall burden of AR has emerged **(Marshall and Levy., 2011)** The extent of usage is expected to increase markedly over coming years due to intensification of farming practices in most of the developing countries **(Van Boeckel et al., 2015)** The main reasons for the use of antibiotics in food-producing animals include prevention of infections, treatment of infections, promotion of growth and improvement in production **(Mathew et al.,2009)** Poultry is one of the most widespread food industries worldwide. Chicken is the most commonly farmed species, with over 90 billion tons of chicken meat produced per year **(Food and Agricultural Organization, 2017).** Alarge diversity of antimicrobials, are used to raise poultry in most countries **(Landers et al., 2012)**. A large number of such antimicrobials are considered to be essential in human medicine **(Mirlohi et al., 2013).**

The indiscriminate use of such essential antimicrobials in animal production is likely to accelerate the development of AR in pathogens, as well as in commensal organisms. This would result in treatment failures, economic losses and could act as source of gene pool for transmission to humans. In addition, there are also human health concerns about the presence of antimicrobial residues in meat **(Darwish et al., 2013)** eggs **(Goetting et al., 2011)** and other animal products **(Addo et al., 2011).**

Bacteria counteract the actions of antibiotics by four well-known mechanisms, namely; enzyme modification, alteration in target binding sites, efflux activity and decreased permeability of bacterial membrane **(Bassetti et al., 2013).** This expression of resistance towards antibiotics by bacteria could either be intrinsic or acquired. Intrinsic resistance is due to inherent properties within the bacteria chromosome such as mutations in genes and chromosomally inducible enzyme production **(Davies, 2007)**, whereas acquired resistance could be due to the transmission of resistance genes from the environment and/or horizontally transfer from other bacteria **(Bassetti et al., 2013).**

Alternatives to antibiotics – Probiotics

While there are now a range of emerging alternatives to antibiotics, perhaps one of the

oldest alternatives – probiotics – is gaining increased scientific interest. Probiotics can be defined as livemicro-organisms which – when given in adequate amounts – confer a health benefit on the host **(Tellez *et al*., 2011)**. The original mechanism of action of probiotics was thought to be "competitive exclusion" **(Nurmi and Rantella 1973)**. There is now an understanding that other mechanisms to explain the activity of probiotics exist - stimulation of both innate **(Farnell *et al*., 2006)** immune regulation **(Li *et al*., 2009)** and even possibly increased apoptosis **(Higgins *et al*., 2011)**. While not universally accepted in all parts of the world, there is now considerable uptake of the use of commercial probiotics for the control of *Salmonella* in the USA **(Tellez *et al*., 2011).**

Alternatives to antibiotics – Prebiotics

Prebiotics are non-digestible feed ingredients that beneficially affect the host by selectively stimulating the activity of one or a limited number of bacteria in the colon **(Gibson and Roberfroid, 1995)**. Prebiotics influence intestinal bacteria and immunity of chickens **(Bozkurt et al., 2014; Kim et al., 2011)**. Major prebiotics mechanisms of action include modulation of gut microbiota by selectively regulating beneficial groups of bacteria by providing food for them **(Hajati et al., 2010)** and by reducing undesired intestinal colonization of pathogenic bacteria, thus improving the integrity of gut mucosa **(Iji et al., 1998)**. Growth performance is the general and direct indicator in poultry as it involves feed utilization and overall effectiveness of poultry production (Ajuwon, 2015).

Alternatives to antibiotics – Bacteriophages

For some time now, there has been active research into the use of bacteriophages to control bacterial diseases of poultry **(Johnson *et al*., 2008)**. In a critical overview of the literature, **Johnson *et al*. (2008)** conclude that phage administration viaaerosol might achieve levels in the respiratory tract that can prevent colibacillosis but not the levels required for treatment. Treatment levels require intra-muscular injection **(Johnson *et al*., 2008),** an option that is not viable in the broiler industry. This suggests that phage therapy for coli-bacillosis has the greatest potential as a preventative measure and not a treatment tool. In terms of *Salmonella*, the results achieved with phage have been very mixed. Reports of significant reductions in *Salmonella* levels following phage treatment **(Atterbury *et al*., 2007)** can be matched by studies that reports of transient reductions only **(Andreatti Filho *et al*., 2007)**. In contrast, phage therapy for the control of *Campylobacter* in broilers holds considerable promise. Several studies **(Atterbury *et al*., 2005; Wagenaar *et al*., 2005; Atterbury *et al*., 2007)** have reported significant reductions in *Campylobacter* levels in treated chickens. There is considerable interest in the concept of the use of phages as a preharvest treatment in which different lytic phages are rotated across different production cycles **(Johnson *et al*., 2008).**

Alternatives to antibiotics – "Natural" feed additives

Fatty acids - especially medium-chain fatty acids –have been long known to have antimicrobial activity against a range of micro-organisms **(Bergsson *et al*., 1998)** Researchers at the University of Arkansas selected caprylic acid (a medium-chain fatty acid with 8 carbons) as a potential natural feed additive **(Solis de Los Santos *et al*., 2008a).** The selection of this acid was based on the knowledge that caprylic acid is likely to be regarded by most regulatory authorities as an acceptable and "natural" feed additive for poultry. Several lines of evidence support this belief. Firstly, caprylic acid is naturally found inhuman breast milk **(Jensen *et al*., 1990).** When used as a food-grade compound, caprylic acid is generally regarded as safe (GRAS) by the US Food and Drug Administration **(Solis de Los Santos *et al*., 2008a).** In the initial work of the Arkansas group the use of caprylic acid at a dose of 0.7% in feed consistently reduced caecal *Campylobacter* counts in a young chick model. If used at a higher dose level (1.4%), there was a reduced feed consumption and body weight (**Solis de Los Santos *et al*., 2008a)**. In subsequent work, the University of Arkansas group has shown that the feed supplementation with caprylic acid at 0.35% and 0.7% can consistently decrease the caecal levels of *Campylobacter* in market-age broilers**.** When used with a 12 hour feed withdrawal program, the feed supplementation with caprylic acid had to be at the 0.7% to achieve a significant *Campylobacter* reduction **(Solis de Los Santos *et al*., 2008b).**

Vaccines – Fowl Cholera

Given that the one of first ever vaccines was the fowl cholera vaccine developed by Louis Pasteur, it is appropriate to look at fowl cholera vaccines – past, present and future – as an example of the potential for novel bacterial vaccines for poultry. In many parts of the world, the only vaccines available for fowl cholera have been killed vaccines– either autogenous or based on the three most common somatic serovars associated with fowl cholera (serovars 1, 3 and 4) **(Glisson *et al*., 2008).** In the USA, live vaccines (the original CU strain or mutants created from the CU strain) have also been used. It is recognised that these CU-type live vaccines have been associated with mortality problems in vaccinated birds (Glisson *et al*., 2008) Now, some 100 years after the original fowl cholera vaccine, the advances in molecular biology have opened up new possibilities of fowl choleravaccines that are based on strains that have been rationally attenuated **(Harper *et al*., 2006).**

Homchampa *et al.* (1992) created a mutant of *P. multocida* in which a keygene associated with the ability of the organism to grow (*in vitro* and *in vivo*) was disabled. Efficacy of this approach of producing a rationally attenuated live vaccine was shown in mice **(Homchampa *et al*., 1992).** This work then enabled the development of two *aro A*mutants (one in a serovar 1 isolate and another in a serovar 3 isolate) which were both shown to provide cross-protection in vaccinated chicken against a serovar 4 challenge **(Scott *et al*., 1999).**

Vaccines – Campylobacter and Clostridium perfringens

The interest in vaccines for the control of necrotic enteritis (caused by *Cl. perfringens*) arises from increasing concerns that the current successful control strategies are based on routine prophylactic administration of antibiotics may not be acceptable to consumers/regulators in the future **(Crouch *et al*., 2010)**. A commercial necrotic enteritis vaccine is now available in many parts of the world. This commercial product is based on a cell-free supernatant toxoid vaccine which is given to breeders. Field trials have shown that this vaccine can result in a significant reduction in mortality and in the typical lesions of necrotic enteritis **(Crouch *et al*., 2010)**. Interest in vaccines for *Campylobacter* form eat chickens is driven by the recognition that *Campylobacter* is a major cause of human causing an estimated 400 million cases of enterocolitisper year around the world **(de Zoete *et al*., 2007).** While not the only source of *Campylobacter*, poultry meat is regarded as a major source of human exposure to *Campylobacter*. To date, there are no commercial vaccines for the control of *Campylobacter* in chickens **(Zhang 2008).** However, there is considerable interest and hope in such vaccines. In part, the interest arises from the fact that significant improvements in human health are possible by reducing, but not necessarily eliminating, *Campylobacter* in chickens. Using models, it has been shown that a 2 log reduction in faecal *Campylobacter* counts would reduce human infections associated with chicken meat by 75%while a 1 log reduction in faecal counts and a 1 logre duction in the processing plant would achieve a90% reduction **(Havelaar *et al*., 2007)**. Hence, the interest in vaccines to achieve a reduction in faecal levels of *Campylobacter* Again, the brightest potential is showing in experimental vaccines produced by molecular biology. Several studies have shown that live attenuated *Salmonella* vaccines that express *Campylobacter* antigens have the capacity to reducecaecal levels of *Campylobacter* **(Wyszynska *et al*., 2004; Buckley *et al*., 2010)**. While the research results to date have been promising, key challenges remain – A) the need for cross-protective antigens to provide as broad a protection as possible for this diverse bacterium and B) the need for rapid, strong and immune response **(de Zoete *et al*., 2007).**

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