The reducing effects of Flavophospholipol on Salmonella shedding and antibiotic resistance in pigs.

Assistance to improve food safety from an unexpected direction

Ir. P.J.G. Oostenbach

Intervet International B.V., P.O. Box 31, NL 5830 AB Boxmeer, The Netherlands

Introduction
The demand for food from pork origin is strongly influenced by the consumers’ concern for healthy and safe food. The topic of food safety mainly concentrates on Salmonella contamination, but in recent years there are public concerns that the use of antibiotic feed additives in animals may give rise to bacterial resistance to human therapeutic drugs, especially those antibiotics that are closely related to human drugs (1 and 16).
The human health authorities and the pig industry world-wide recognize the implications of Salmonella infections in humans and pigs as it negatively affects food safety. The spread of Salmonella spp during pig production is complex as shown in a simplified way in figure 1.
This demonstrates clearly that no single solution may be expected.
It is of utmost importance to realize that the efficacy of a Salmonella Control Program does not solely depend on the implementation of one or two preventive measures.

Simultaneous implementation of a adequate monitoring program, in case of observed contamination followed by corrective measures, and adequate biosecurity
is essential. Another important, sometimes neglected phenomenon is the animals' own natural defence mechanisms, that are formed by the immune system and the intestinal microflora that can both provide protection against Salmonella infections. This phenomenon is known as Competitive Exclusion and was first described by Nurmi en Rantala (10). The underlying mode of action(s) is (are) still not fully understood. Most probably it is a combination of several factors, among which:

- Production of agents by certain beneficial organisms that have a negative influence on the growth capacity of other harmful or at least unwanted organisms (2 and 5). Recently van der Wielen et al (15) concluded that volatile fatty acids (in the undissociated form) are responsible for the reduction in numbers of Enterobacteriaceae in the ceca of broiler chickens during growth;
- Competition for substrate;
- Competition for attachment sites;
- Immunomodulation.

Recent studies on Flavophospholipol, registered as AMGP for pigs, describe a reducing effect on Salmonella shedding and antibiotic resistance. This product was not affected by the EC ban on AMGP's as it is not related to any antibiotic used for veterinary or human therapy.

**Product characteristics of flavophospholipol**

Flavophospholipol (Flavomycin®), belonging to the antibiotic-class of the phosphoglycolipids, is licensed as a digestive enhancing antibiotic by the regulatory authorities in the EU, the USA and most countries world-wide. Due to its limited efficacy against human bacteria and its poor pharmaceutical properties it is not related to any antibiotic currently in use or under development for the treatment of human or animal diseases. Therefore it was not affected by the decision of the EC to ban the digestive enhancing antibiotics are related in any way to antibiotics used for human or animal therapy.

The very limited direct antibacterial activity is restricted to the gram-positives. The enzyme glycosyltransferase, that plays an essential role in the synthesis of the cell wall of this group, can not distinguish between Flavophospholipol and the natural compound. This results in an unstable cell wall, leading to the death of this cell. In gram-negatives glycosyltransferase plays no role, due to the different cell wall structure. However when a plasmid bridge (pylus) is formed it’s biosynthesis is disrupted in a similar way, leading to the death of the donor-cell. This plasmid bridge plays an essential role during the transfer of genetic information on antibiotic-resistance from one bacterium to another. In this way Flavophospholipol prevents this genetic transfer and actually reduces the number of resistance carrying bacteria. This reducing effect on plasmid-bound antibiotic resistance has
already been described since the early 70’s (6, 7, 8, 9 and 14). Of more recent date is the publication of Riedl et al (12).

**Reduction of Salmonella shedding**
The Fifth Amendment of the Feed Additive Directive (70/524/EEC) requires submission of information on the possible effect of feed additives on the excretion of food-borne pathogenic bacteria like Salmonella and Campylobacter. This study (3) was conducted in broilers to satisfy the requirement for the commercial product Flavomycin®. The results show that Flavomycin® reduced significantly (P< 0.05) the level of Salmonella-shedding and the number of broilers shedding S.e. at slaughter age. Recently Schleifer et al (13) observed the same effect under US-field conditions. These results confirm older studies in pigs (6) in which a reduction of the duration and prevalence of salmonella shedding was observed. In this study a non-medicated control group was compared to a group that was fed a Flavomycin-supplemented feed. At 6 weeks of age all pigs were inoculated by gavage with 2.5x10¹¹ of a multi-resistant Salmonella typhimurium strain. Fecal samples were taken from all pigs on days 2, 4, 7, 10, 12, 14, 21, 28, 35, 42 and 49. The percentage of pigs shedding Salmonella is summarized in figure 2.

Comparing the proportion of all animals having positive Salmonella-counts by group for all time periods illustrates that Salmonella was more prevalent (P < 0.01) in the non-medicated group for the 2- to 35-day period. Similar results were obtained in calves (7).

**Reduction of antibiotic resistance**
The concern on antibiotic resistance is that the plasmids carrying this antibiotic resistance may be transferred by a plasmid bridge (pylus) from non pathogenic intestinal bacteria in animals to human pathogens. Flavophospholipol interferes in the biosynthesis of this pylon and therefore prevents this genetic transfer and actually reduces the number of resistance carrying bacteria. As cited before this reducing effect of Flavomycin® on plasmid-bound antibiotic resistance has already been described since the early 70’s. Of more recent date is the publication of van den Bogaard (4). The results are summarized in figure 3 and 4.
These results indicate clearly that Flavophospholipol reduces significantly vancomycin resistance in enterococci (VRE) and antibiotic resistance in E.coli.

Discussion / Conclusions
The above mentioned data clearly indicate that inclusion of Flavophospholipol in pig diets might be an efficacious instrument to reduce the level of Salmonella-infections during production in an infectious environment. Combination of the use of Salmonella vaccines at breeder and fattening level and the inclusion of Flavophospholipol in pig diets could be a synergetic beneficial instrument in a Salmonella Control Program in addition to an adequate monitoring program, in case of observed contamination followed by corrective measures, and adequate biosecurity. A similar approach has been described for poultry (11). However Salmonella is only one aspect of Food Safety. Another aspect is the level of antibiotic resistant organisms in animal production as this may be a risk that could influence the efficacy of human antibiotic treatments. Flavophospholipol is supported by sufficient scientific evidence that it does not increase the level of antibiotic resistant organisms in animal production. In fact a reducing effect is more likely.

References


