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Denmark, antibiotic alternatives, and the US industry

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Summary

The pig industry must use antimicrobials more conservatively than in the past, and that will require a new paradigm. It will not require complete elimination of antimicrobials from pig production. When Denmark eliminated the use of antimicrobials as growth promoters for finishing pigs, results included the anticipated reduction in resistance of some bacteria to some antimicrobials, and no discernable reduction in pig performance. Elimination of antimicrobial growth promoters from nursery diets was strikingly unsuccessful. Reduction of use of antimicrobials, which are powerful promoters of good health, directs attention to other means of improving pig health and performance. We have a rich supply of feed ingredients that may be useful. The North American pig industry has already widely adopted zinc oxide and copper sulfate, milk products, and spray-dried animal plasma, and we use acids, mannan oligosaccharides, direct-fed microbials, fructo-oligosaccharides, and egg immunoglobulins to a lesser extent. These products and others appear promising, but in several cases we need a clearer understanding of their physiological effects and their effects on both performance and health of pigs in commercial production.

Introduction

The use of antibiotics (and other antimicrobials) in animal production is the focus of intense debate. The future is uncertain, but one thing is clear—the paradigm must change. The pig industry must view antimicrobials differently and use them more conservatively than in the past, in response to pressures from both regulators and markets.

Any use of an antimicrobial brings an ecological competitive advantage to bacteria that are resistant to the effects of that antimicrobial and causes their numbers to increase. Thus, use of antimicrobials does not cause resistance, but does increase the prevalence of resistance. Most of the antimicrobial resistance that causes problems in human medicine is the result of use of antimicrobials in human medicine. However, it seems likely that use of antimicrobials in animals makes a small contribution to the problem, and that is the reason for the pressure to reduce the amount of antimicrobials used in animal production.

The European Union has tightened restrictions on antimicrobial use much more aggressively than has the United States. Of special interest, Denmark has completely eliminated the use of antimicrobials as growth promoters in animal production, and the Danish experience may be useful to the rest of us as we contemplate tighter restrictions on the use of antimicrobials. Note that the dramatic step taken in Denmark is strikingly less severe than complete elimination of antimicrobials from animal production, which would be unwise.

The Danish experience and the US industry

Denmark's termination of antimicrobial use for growth promotion occurred in step-wise fashion, with the final steps occurring in a very different environment of antimicrobial use than now exists in the United States. All interpretation of the Danish experience should consider the fact that the Danish industry had a much smaller selection of antibiotics at its disposal than we have in the United States. For that reason, termination of antibiotic use for growth promotion would be a bigger step for us than it was for Denmark.

The following key events occurred in Denmark:

- 1995: Denmark started monitoring antibiotic resistance.
- 1997: Denmark started an intensive research program on the discontinuation of use of antimicrobial growth promoters, including a study of alternatives.
- December, 1997: The European Union (EU) banned avoparcin.
- January, 1998: Denmark banned virginiamycin for growth promotion.
- February, 1998: Denmark stopped using antimicrobial growth promoters in cattle, poultry and finishing pigs (> 35 kg).
- July, 1999: The EU banned four antimicrobial growth promoters (tylosin, spiramycin, bacitracin, virginiamycin).

- September, 1999: The EU banned olaquindox and carbadox.
- December, 1999: Denmark stopped using antimicrobial growth promoters in weaners (< 35 kg).

When Denmark banned the use of antimicrobial growth promoters in nursery pigs (December, 1999), it effectively eliminated the use of only flavomycin and avilamycin. However, the timing of the events confounds the cessation of use of these products with the elimination of the quinoxalines (olaquindox and carbadox) and, to a lesser degree, with the elimination of the four growth promoters in July, 1999.

The striking thing about the termination of use of antimicrobials for growth promotion in finishing pigs is the absence of dramatic changes. There was no discernable increase in the amount of antimicrobials used for disease treatment (DANMAP, 2003), although this comparison is quite insensitive. Similarly, there were no obvious effects on growth performance or mortality (according to data from a national Efficiency Control Program that collects data from about 1,500 producers; Callesen, 2002). There were reductions in the prevalence of resistance to some antimicrobials in some bacteria (DANMAP, 2002), the effect that was desired.

The lack of large effect of termination of antimicrobial growth promoters in finishing pigs in Denmark may be explainable by a lack of beneficial effects of the antimicrobials in question. There may have been subtle effects that were too small for detection, or were in measures not examined (e.g., variation in performance among pigs in a group). Alternatively, Danish producers may have introduced adaptive mechanisms to effectively compensate for the loss of antimicrobial growth promoters.

The experience after termination of antimicrobial growth promoter use in nursery pigs was very different. The use of therapeutic antimicrobials went up (DANMAP, 2003), the growth rate went down, feed efficiency worsened, and the death loss increased (Callesen, 2002). There was an increase in the prevalence of tetracycline resistance in *Salmonella typhimurium* taken from pigs at slaughter, and also from ill humans (DANMAP, 2002). Termination of antimicrobial growth promoter use in nursery pigs was not successful by any measure.

Recent controlled experiments in Denmark showed an average growth rate response of 10.8% to antimicrobial growth promoters in nursery pigs (Kjeldsen, 2002), but the growth rate declined only 2.6% nationally upon termination of antimicrobial growth promoter use. The difference may have occurred because producers introduced other compensating technologies. There are no data to confirm that suggestion or to indicate what technologies may have been adopted beyond the increased use of therapeutic antimicrobials. I suggest that other possibilities include adoption of all-in/all-out pig flow, increased weaning age, more aggressive biosecurity and sanitation measures, and addition of organic acids to the diet, among other possibilities. Some of these measures are expensive. Given the lack of information about what changes producers actually made and the cost of those changes, I find it impossible to estimate with confidence the increased production cost associated with termination of antimicrobial growth promoters.

Antibiotic alternatives

Antibiotics are powerful tools in pork production, especially for maintenance of pig health. As we reduce our use of these powerful tools, we need to make the appropriate adaptive responses. This paper will focus on physiologically active feed ingredients other than antibiotics that we may use to improve pig health and performance. However, an appropriate response to reduced use of antibiotics is much broader than feed ingredients, and includes such things as production systems (pig flow), biosecurity, sanitation, vaccination, and disease eradication.

The term "alternatives to antibiotics" may be interpreted to suggest low-inclusion, non-antibiotic feed ingredients that do what antibiotics do. It is unlikely that such products exist. However, certain physiologically active feed ingredients may be useful in modifying the gut environment in such a way that they improve growth performance and/or resistance to enteric diseases. These products may be useful either in the presence or the absence of antibiotics. They are likely to be more useful in the nursery phase than in the finishing phase because of the greater challenge of keeping young pigs healthy. We are already using some of these products routinely, but there are others that may be useful but that we have not yet exploited. The following is a partial list.

Zinc oxide and copper sulfate

The use of high levels of zinc oxide (usually > 2,000 ppm Zn) and/or copper sulfate (> 125 ppm Cu) is very widespread in early nursery diets for control of diarrhea and for growth promotion. They are effective.

Milk products

When we first started adding complexity to pig starter diets in the 1970s, spray-dried whey was the first special ingredient used widely in such diets, and we continue to use large quantities of it. Whey provides both lactose and proteins. Lactose is a dietary energy source that is easily utilized by the young pig, but it may be more than that. Lactose appears to be a prebiotic—a dietary ingredient that favors the proliferation of certain bacteria in the digestive tract because it is a preferred nutrient source for those bacteria. It appears to stimulate the growth of *Lactobacilli* and other bacteria that are sometimes considered beneficial in the gut. It is now common practice to specify a minimum constraint on the lactose level in nursery diets (Tokach et al., 1997).

There may be also benefits from the milk proteins, including immunoglobulins.

Spray-dried animal plasma

Spray-dried animal plasma is used widely in diets for pigs immediately after weaning. It likely contains many components that may have physiological activity. The specific modes of action of plasma are not known, although some evidence suggests that it affects the immune system (Touchette et al., 2000a, b) and the populations of *Lactobacilli* in the gut (Torrallardona et al., 2003).

A meta-analysis conducted in The Netherlands (Van Dijk et al., 2001) showed that inclusion of spray-dried animal plasma in the diet of weaned pigs in several studies increased the growth rate by an astounding 27%, on average. It is rare to find a feed ingredient that causes such a large increase in growth rate.

Acids

Diet acidifiers are used much more in Europe than in North America, although much of the early research on organic acids was done in the US (Easter, 1988). Some studies (Burnell et al., 1988; Allee et al., 1999) have shown that acids are less beneficial in diets that include milk products than in simpler diets, and that observation has diminished the interest in practical use of acids in North America. We are currently investigating possible reasons for the proposed lack of additivity of organic acids and milk products. Perhaps acids will become important components of nursery pig diets in North America.

Mannan oligosaccharide (MOS)

This product, derived from yeast cell walls, produces a small but clear increase in growth rate in weaned pigs (Miguel et al., 2002). Its mode of action is unclear, but it may be binding of certain bacteria to prevent their adhesion to the gut wall. It has bigger effects in pigs that are apparently less healthy.

Direct-fed microbials (probiotics)

Direct-fed microbials, often called probiotics, are fed to animals in an attempt to encourage the proliferation in the gut of the specific bacteria fed. They have been available for decades. There continues to be a significant amount of research reported on such products. It is dangerous to draw general conclusions about the effects of direct-fed microbials from measured effects in a few, because each product could have different effects in the gut.

Fructo-oligosaccharide (FOS)

Fructo-oligosaccharides are short chains of fructose. These oligosaccharides are prebiotics, preferred substrates for certain intestinal bacteria, primarily *Bifidobacteria*, which are often considered to be desirable. There is evidence that this product causes the expected change in gut microbial populations, and may improve performance (Howard et al., 1999).

It seems reasonable to combine a probiotic with a prebiotic that favors the probiotic organism(s), but we don't have much data on such combinations.

Note that mannan oligosaccharides and fructo-oligosaccharides have similar names but are completely different products, with different perceived modes of action. Fructo-oligosaccharide is a chemically-defined product, varying only in chain length, while mannan oligosaccharide is a much more complex product than its name suggests, being a processed part of the yeast cell wall.

Egg immunoglobulins

Hens can be immunized against specific porcine pathogens, and immunoglobulins from their eggs prepared into a feed additive. A battery of hens immunized against different pathogens supports development of a product that may potentially provide passive immunity to several diseases. Early data suggest that these products may improve performance and resistance to disease (Godfredson-Kisic and Shipp, 2000). The egg immunoglobulins are sometimes combined with spray-dried plasma. Perhaps such products will eventually be prepared for specific combinations of disease, or even for specific farms.

Herbs, spices, botanicals, and essential oils

Herbs and spices are parts of specific plants that have properties deemed desirable for medical use, flavor, odor, or food preservation (Wenk, 2000). Botanicals are drugs made from plants. Essential oils are extracts of plants in which the active components are concentrated and are used largely in the manufacture of perfumes, flavors, and pharmaceuticals. These plant products are considered to have several potential functions when added to animal diets, including enhancing palatability and, therefore, feed intake, altering microbial populations in the digestive tract, and serving as antioxidants in the tissues (Wenk, 2000). There is an expanding body of data on the effects of adding these products to animal diets, but we need more convincing evidence of benefits. Each compound or product must be evaluated, as they all may have different effects.

Competitive inhibition products

Bacteria are harvested from the intestine of a healthy adult animal, propagated in the laboratory, and given orally to a young animal, often immediately after birth. The purpose is to allow these "desirable" bacteria to occupy the binding sites on the gut wall, and thereby to prevent attachment of pathogens. Laboratory studies have shown protection from disease challenges (Anderson et al., 1998).

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