In-Feed Antibiotics–Some of the Issues
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Why has this debate lasted 50+ years?
Availability of antimicrobials for use in human medicine, veterinary medicine food animal production is a privilege rather than a right. Given the current high level of scrutiny of antimicrobial use in all arenas, it is remarkable to think that in the 1950s antimicrobials became available for over-the-counter sale and use in food animal populations in many developed countries. Moreover, low-dose long duration feeding of antimicrobials was widely adopted in food animal production after it was recognized that this could enhance growth rate and feed efficiency in poultry and swine. At that time, the phenomenon of antimicrobial resistance emerging as a consequence of antimicrobial use was already well established (albeit of less immediate clinical consequence). It is also worth noting that unrestricted over-the-counter sale of antimicrobials remains the norm for use in both humans and animals in many developing countries. Few would argue that this is wise, and the occurrence of imprudent use is inevitably a function of availability. However, specifically with respect to animal uses, it has been difficult to establish that this has been harmful in terms of the incidence of clinical treatment failures in human infections. Until now there is no published risk assessment linking an increased risk of human clinical treatment failures with any specific antimicrobial use in food animals. A recent review of interventions employed to reduce antimicrobial use food animals in Denmark was accompanied by neither data nor claims of measurable benefits to human health consequent to this achievement. This enduring uncertainty over the public health consequences of antimicrobial use in animals has frustrated groups who have avidly pursued greater regulation of antimicrobial use in food animals in the USA.

There is no dispute that antimicrobial resistance is a pressing problem in human medicine, although estimates of the public health costs attributable to antimicrobial resistance are uncertain. Costs are incurred as increased treatment costs and case fatality rates, and as infections in people treated with antibiotics that might otherwise not occur (i.e., in the absence of resistant organisms). There is some dichotomy of emphasis in the medical literature on antimicrobial resistance. Analyses by infectious disease experts who are focused on the control of antimicrobial resistance in human medicine seldom refer to foodborne pathogens such as Salmonella and Campylobacter or the importance of animals as sources of resistant organisms. A survey of senior medical microbiologists in Europe about the relative importance of bacterial species to the resistance problem ranked these organisms 15th and 18th respectively out of 20 organisms listed. In contrast, authors writing on antimicrobial use in agriculture primarily focus on these two organisms, but rarely provide meaningful context about their relative contribution to the overall problem of treatment failures in human clinical medicine. One widely cited modelling study estimated that antimicrobial resistance in Salmonella and Campylobacter in the USA results in an additional 12 deaths annually from Salmonella infections and 95 hospitalizations with C. jejuni infections. All incidents of illness and death are regrettable, but these modest estimates position antibiotic resistant foodborne pathogens substantially below lightning strike or dog bites as public health concerns in the USA. Foodborne disease and antimicrobial resistance are major and costly human health problems, but the contribution of the former to the latter is arguably minimal. An extensive North American review stated that “the
extent to which antibiotic use in food animals produces clinically important antibiotic resistant infections in humans is unknown. After almost 5 decades of debate, the impact of antimicrobial use in food animals on human health is still undecided. To further muddy the waters, some efforts at quantitative assessment of the risk of human treatment failures related to specific practices of animal use have concluded the risks to be ‘vanishingly small’. In addition some studies have posited possible human health benefits through improvements to animal health that translate into less carcass contamination during processing.

**Banning growth promotants—strategic reduction or low-hanging fruit?**

Antimicrobials are important tools for ensuring the health, welfare and productivity of pigs raised for food. Banning of antimicrobial growth promotant use in Denmark, and subsequently more widely in the EU, has encouraged many entities to seek more restricted availability of antimicrobials for food animals in the USA. I have heard medical clinicians state the rather anthropocentric view that any antimicrobial use in animals is imprudent, but ‘middle of the road’ people accept that animals suffering from bacterial infections should be treated with antimicrobials (the frequency of antimicrobial use in companion animals provides reasonable support for this). As we traverse the spectrum of ‘therapy-metaphylaxis-prophylaxis-growth promotion’ uses, enthusiasm for antimicrobial use in animals will understandably decline. If we assume that any reduction of antimicrobial use is desirable (i.e., less is better) it seems logical to eliminate uses that are ‘less necessary’ or less justifiable in terms of benefitting animal health and welfare. A more strategic approach would require understanding of the relative consequences (in terms of prevalence of resistant organisms with implications for public health) of these different strategies for deploying antimicrobials in food animal populations. There is a considerable body of published literature that claims that ‘growth promotant’ uses are of particular concern regarding resistance.

We are now finalizing an appraisal of the literature cited in four specific reviews (the FDA Guidance for Industry #209; the Preservation of Antimicrobials for Medical Treatment Act; the Pew Commission on Industrial Farm Animal Production report; and the Keep Antibiotics Working Group annotated bibliography). These documents are at the centre of discussions on regulation of antimicrobial use in food animals in the USA. The FDA’s Guidance for Industry #209 suggests that some uses of low-level antimicrobials administered in feed are “injudicious”. The Preservation of Antibiotics for Medical Treatment Act calls for the discontinuation of all non-therapeutic or routine uses of certain classes of antimicrobials in animal agriculture, and has been introduced into Congress in several recent sessions. The specific objective of our study was to critically appraise the literature on antimicrobial use in pork production to determine strength of evidence that long term use of specific levels of specific antimicrobial compounds in feed contributes greater risk to public health than other food animal antimicrobial uses.

Out of over 400 references in these sources, our initial inclusive screening identified 154 papers as likely to be relevant to our core objective. These were then categorized as 1) descriptive (n = 48) if they included data on antimicrobial use or resistance without comparison groups; 2) analytical (n = 37) if the study included data on antimicrobial use or resistance and at least one comparison between groups; or 3) reviews (n = 69) if they did not present original data but summarized previous work on antimicrobial use or resistance. Two evaluation tools (one for original studies, one for reviews) were developed for systematically evaluating individual papers. Only 12 of the cited papers reported research data directly relevant to the specific purpose of this study (comparing the impact of low dose antimicrobial use to other modes of use). These papers
were reviewed in depth, and only one study in poultry presented primary evidence of a statistically significant advantage for therapeutic mode of administration over a low dose administration in feed with respect to the resistance outcomes measured. The descriptive studies, not having comparison groups, were not designed to enable comparison of treatments, and many reported only antimicrobial use or resistance data. Nonetheless, it is notable that despite the failure to measure both antimicrobial use and resistance in these descriptive studies, 16 of the 36 implicated antimicrobial use in antimicrobial resistance in the discussion or conclusions.

The vast majority the papers cited by these key sources contain no primary data to support the contention that low dose antimicrobial use exerts more selection pressure for resistant bacteria than therapeutic uses, or augments public health risks from antimicrobial resistant organisms. It is notable that these key sources cited a large proportion of review studies. Detailed examination of 37 reviews most closely related to our appraisal found that none employed systematic review methods but were narrative reviews or reports. Only one stated the search methods used to identify cited sources, and only one (different) review specified inclusion and exclusion criteria for the studies they cited. No reviews stated any criteria of validity assessment used in the selection of studies cited, or indicated any measures were taken to identify or address potential biases. Only three of the reviews discussed validity in analyzing studies or drawing inferences in their review process, and no reviews discussed potential limitations of their study. Collectively, these 37 sources cited 1,869 publications (ignoring duplications) of which 1012 (54.2%) were determined to be studies providing original data. That is, almost half the sources cited in the reviews evaluated were other reviews and reports, rather than primary sources. In summary these reviews in general reiterate the most storied examples linking antimicrobial use in animals to the emergence of resistance, but provide neither explicit information contrasting the impact of low-dose, long duration (growth promotion) administration relative to other methods of administration, nor novel insight into understanding this question.

Currently available evidence is inadequate to provide any meaningful comparison of different modes of antimicrobial resistance in relation to the emergence of antimicrobial resistance in pathogens or commensals in commercial swine populations. In the absence of evidence indicating any differential effect among modes of antimicrobial use in food animals, the conservative position would be that reducing aggregate use of antimicrobials is the most appropriate goal. FDA Guidance 209 will likely lead to the removal of most growth promotant claims in the USA within 3 years.

**Being part of the solution**

The process of weighing policy options related to antimicrobial use in food animals should be evidence based and arguably should include consideration of animal health and welfare, and environmental impacts, in addition to human health outcomes. As a general assumption, it is reasonable to assume that reduction in aggregate use of antimicrobials will lessen the pressure of selection for resistant organisms. It is also plausible that different patterns of use of antimicrobials (e.g., selection of drug; route of administration; dose; duration) will exert differential selection pressures both qualitatively (organisms impacted) and quantitatively. In food animal settings, these myriad of different options will presumably have diverse implications for public health (assuming all are non-zero). However, the pharmacoepidemiology of induction and dissemination of antimicrobial resistance is complex and poorly understood, and particularly in relation to public health risks linked to animal food products. Optimization of antimicrobial use in food animals will require definition of practices of greatest value to maintaining animal
health and well-being, as well as practices that are more or less likely to select for antimicrobial resistant organisms of public health importance.

We can anticipate on-going pressures for reducing antimicrobial use in all food animal industries into the future. The consequent impacts on swine health and production will depend on the nature of future restrictions. Both the Swedish and Danish bans on antimicrobial growth promotants in pigs had measurable consequences for pig health, most notably the increased incidence of enteric disease in weaned pigs and increased need for therapeutic antimicrobials. However, in both countries impact on finishing pigs appears to have been minimal. Recognition of the particular vulnerability, and therefore particular needs, of the weaned pig in relation to infectious disease control and prevention needs to be emphasized in discussions of strategic antimicrobial use in swine. In my opinion, the most reasonable path forward appears to be elimination, based on the precautionary principle, of in-feed use of antimicrobials for production purposes in finishing pigs, and preservation of broad treatment and prevention options in weaned pigs (say up to 10 weeks of age). This would maintain flexibility in health management during the most crucial 6-7 weeks of post-weaning life, yet should substantially reduce aggregate antimicrobial use in the final 4 months or so when feed intake is highest and use occurs most closely to the point of marketing and human consumption. A voluntary initiative by industry to implement this strategy would have been a reasonable strategy to counter the image of intransigence of industry players to cooperate in the goal of reducing antimicrobial use. Apart from the possibility of demonstrating good will to the public, this may also have provide some leverage for the future encroachments on more essential modes of use in large populations.

The goal of reduced antimicrobial use in the future should not be pursued without regard to relatively predictable costs to piglet health and welfare. However, desperate attempts to preserve the status quo regarding antimicrobial use are unlikely to be successful and may be counterproductive. Continued efforts to upgrade facilities and management to enhance pig health need to be pursued. We should expect greater involvement, direct responsibility, and accountability of veterinarians in optimizing antimicrobial use in swine herds; some management changes (such as older weaning age); and some innovation necessary to offset the health impacts of restricted antimicrobial availability.

REFERENCES