RESEARCH ABSTRACT

PUBLIC HEALTH/WORKER SAFETY

Title: Critical appraisal of evidence that low-dose, long term (growth promotion) antimicrobial use augments public health risks from antimicrobial resistant organisms – **NPB #11-024**

Investigator: Peter Davies

Institution: University of Minnesota

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Scientific Abstract

The purpose of this project was to critically appraise evidence related to the relationship between antimicrobial use (AMU) in food animals and antimicrobial resistance (AMR) cited in 4 key documents that support greater regulatory restriction of low dose antimicrobial use in the USA (FDA Guidance for Industry #209[a]; Preservation of Antimicrobials for Medical Treatment Act; Pew Commission Report on Industrial Farm Animal Production report; Keep Antibiotics Working Group annotated bibliography). The specific goal was to 'critically appraise the literature on antimicrobial use in pork production to determine the strength of evidence that long term use of certain levels of specific antimicrobial compounds in feed contributes greater risk to public health than other food animal antimicrobial uses'. Among the 154 references cited by these sources that were deemed relevant to AMU and AMR in food animals, only 37 (24%) were original studies that included some analysis of primary data (termed 'analytical studies'). The remaining citations were either original studies that presented data on AMU or AMR but did not make comparisons among groups (termed 'descriptive studies'; N = 48; 31%), or review papers or reports that did not present original data and analysis (termed 'review studies'; n = 69; 45%). The studies were evaluated using appraisal tools (one for analytical and descriptive studies, one for reviews) developed to enable systematic evaluation of the individual papers.

Only 12 (8%) of the cited papers were analytical studies that included primary research data relevant to the specific purpose of this project (comparing the impact of low dose antimicrobial use to other modes of antimicrobial use in food animals). These papers were reviewed in depth to identify strengths and weaknesses of the papers, and assess the evidence base for the conclusions drawn. Only one analytical paper (0.6% of the 154 relevant cited papers) directly compared the effects of a low-dose and therapeutic dose of antimicrobials administered to food animals (poultry) on the prevalence of AMR. From the perspectives of causal inference or effect estimation, the 48 descriptive studies cited by the 4 key documents were collectively uninformative regarding the association of low-dose long term administration of antimicrobials to food animals with AMR. In both the analytical and descriptive studies which reported on AMU, both the measurement and recording of AMU were found to have shortcomings in many studies. For example, only 9 (6 analytical, 3 descriptive) studies provided comprehensive details of the drug, dose, route, and duration of administration of the antimicrobial(s) used.

[a] The original appraisal assessed the Draft for FDA guidance 209. Additional references cited subsequently in the final guidance document, but not the draft, were later evaluated in the final revision of this report.

Appraisal of review studies focused on 37 reviews that specifically referred to AMU or AMR in their summary or stated objectives. None of the 37 reviews employed systematic review methods, but were narrative reviews (29) or reports (8). Only one review included the search methods used to identify cited sources, and only one (different) review specified inclusion and exclusion criteria for the studies they cited. Only 3 of the reviews discussed validity in analyzing studies or drawing inferences in their review process, and none discussed potential limitations. Collectively, these 37 sources cited 1,869 publications (ignoring duplications) of which 1,012 (54.2%) were determined to be original studies providing original data. The review papers appraised generally reiterated a small number of familiar examples linking antimicrobial use in animals and AMR. The majority of these examples related to antimicrobials used only therapeutically in the USA (e.g., fluoroquinolones), or antimicrobials that have never been available in the USA (avoparcin, nourseothricin). Collectively, the review studies presented negligible evidence of any differential effects among specific modes of antimicrobial use in swine production in selecting for antimicrobial resistance.

Due to the dearth of evidence that specifically addressed our core question (comparison of low-dose/long term use of antimicrobials in feed with other modes of AMU), we expanded the scope of the project to identify other original research studies that might inform this question. This process was not comprehensive, but adopted four strategies that identified 20 original studies, which were assessed in detail. Generally, these sources reported positive associations between aggregate AMU and AMR, but also bear testimony to the biological complexity of these relationships and the challenges of researching it. Five experimental studies specifically designed to compare low-dose/long term use and therapeutic uses in pigs generally reported no difference among treatment groups, or trends of more resistance among groups receiving therapeutic regimens. We remain unable to identify any convincing body of evidence indicating that low-dose/long term administration of antimicrobials is more likely to promote AMR than use by other modes.

We noted that none of the 4 key sources cited any published quantitative assessments of the risk of human treatment failures related to specific practices of AMU in food animals. However, several quantitative risk assessments addressing low-dose/long term AMU have estimated the risks to be extremely small. Furthermore, a small number of recent studies of both pigs and poultry have found that use of antimicrobials at low doses to control endemic diseases in food animals can be associated with improvements to animal health that translate into less carcass contamination during processing. It is inferred that this could further translate into human health benefits through reduced risk of exposure to pathogens. This small body of work needs to be expanded as it suggests that some unintended and adverse human health consequences could ensue from a non-strategic prohibition of low-dose AMU in food animals.

Currently available evidence is inadequate to provide any meaningful conclusion regarding the relative effects of different modes of antimicrobial use on the emergence of antimicrobial resistance in pathogens or commensals in commercial swine populations. The precautionary principle underlying regulatory changes in Europe remains the centerpiece of arguments for similar regulation in the USA, and FDA guidance 209 will likely lead to the removal of most growth promotant claims in the USA within 3 years. Our analysis suggests that this is not an optimal regulatory intervention. Data from Denmark shows that the lowest rate of aggregate antimicrobial use in the Danish swine industry occurred in 1999 after the withdrawal of growth promotants from finishing pigs, but before their withdrawal from weaned pigs. 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, and its regulation, in swine. We are of the opinion that the available scientific data, and history of experiences in Europe, suggest that the most strategic path forward would be elimination, based on the precautionary principle, of AMU for production purposes in finishing pigs, but preservation of all existing therapeutic, metaphylactic and prophylactic options in weaned pigs (until 10 weeks of age). This would maintain flexibility in health management during the most crucial phase of swine production, yet should substantially reduce aggregate antimicrobial use with much less impact on animal health and welfare. However, given the likely implementation of proposed changes, industry needs

to focus on the expected negative impact on pig health, particularly related to enteric disease in weaned pigs, and the likely constraint of manpower of food animal veterinarians that will be necessary to provide greater veterinary oversight of all antimicrobial use in food producing animals.