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A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production

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NOTE: This briefing note represents work in progress. The authors would welcome feedback and any additional literature not identified or not covered in this review.

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Executive Summary

Antimicrobial drugs play an important role in treating diseased animals, but their non-therapeutic use in food animal production undermines efforts to curb antimicrobial resistance. The quantity of antimicrobials used for food animal production is significant compared to human use and on an upward trajectory. Between 2010 and 2030, an Organization for Economic Cooperation and Development (OECD) analysis projects antimicrobial consumption in food animal production will climb by 67 percent—two-thirds of this increase coming from the larger number of food animals in production and one-third resulting from the switch to more intensive animal production systems. Non-therapeutic antimicrobial use in food animal production has largely been driven by perceived economic benefits, including greater feed efficiency and growth, decreased time to market as well as lower mortality and morbidity of food animals. This use, however, has generated significant concern due to its contribution to antimicrobial resistance.

This briefing note provides an overview of the published literature on costs associated with lowering antimicrobial use in food animal production and of switching to alternative modes of production across livestock sectors and countries. Using a structured search of the literature, 24 studies providing economic costing data on production-purpose and prophylactic antimicrobial use were identified. Only studies that included costing figures of economic effects were reviewed. Studies identified were limited to the United States and Europe, largely focused on intensive operations, and provided insight on economic impacts at the animal, farm, and market level. Considering experimental and observational data, these studies show wide variation in the economic effects of curbing non-therapeutic antimicrobials across the animal, farm, and market levels. For example, one of the more comprehensive studies across livestock sectors, a 2015 U.S. Department of Agriculture Economic Research Service (USDA/ERS) analysis, examined the impact of phasing out non-therapeutic antimicrobials in hogs and broilers as well as beef and dairy cattle. Using an assumption that such antimicrobial use would increase productivity by 1 to 3 percent, the USDA market model demonstrated that wholesale prices would rise by 1 percent and output would fall by less than 1 percent. The implications of a market ban had the greatest impact on price and quantity in the first year, but declined by the fifth year. Beyond static market analyses, dynamic modeling at the market level is needed to assess how producers will change their production practices to offset the costs of curbing use of non-therapeutic antimicrobials and how consumers might be willing to pay higher prices on food animal products raised without such antimicrobial inputs. A full accounting of externalities from industrial food animal production though goes beyond the scope of resistance discussed here.

Alternatives to non-therapeutic antimicrobials range from changing production practices such as altering the weaning period or improving hygienic conditions to using substitutes such as vaccines or feed additives. Changes in production practices may require initial capital investment costs and moderate resource inputs over time. Nevertheless, in countries such as Denmark, Sweden, and Netherlands, which are among the world's largest exporters of food animal products with largely intensive operations, bans on growth-promoting antimicrobials have not adversely affected productivity over time – in fact, productivity levels have been maintained or been increased. This has been attributed to changes in production practices and use of antimicrobial alternatives that have decreased the need for such non-therapeutic uses.

We also provide a preliminary assessment of what data gaps in costing exist, what data elements might be more pivotal for policymaking and economic decision-making, and how these gaps might be filled. The shortcomings of existing data include gaps in surveillance data, costing data, and data on production practices and characteristics. Economic studies from high-income settings such as the United States and Europe must be complemented by studies conducted in resource-limited settings, and local costing data for existing and alternative production practices would be important to capture. Even in industrialized countries, a paucity of antimicrobial use data complicates relating resistance patterns observed in bacteria to patterns of drug administration. At the same time, while such data collection might inform the best approach to implementing changes, it need not delay taking steps to remove non-therapeutic use of antimicrobials in animal agriculture.

To help focus efforts to assess the costs of transitioning away from the non-therapeutic use of antimicrobials, we might consider whether identifying critically important antimicrobials, examining the mode of agricultural production, or looking for geographic hotspots might be strategic. By identifying the classes of critically important, new antimicrobials, these drugs might be reserved for human use. Along the same lines, the emergence of resistant pathogens induced by the use of other antimicrobials might prompt regulatory removal of such drugs from specific veterinary uses. However, co-resistance to multiple classes of antimicrobials makes it imperative to reduce non-therapeutic use of antimicrobials across the board.

Existing evidence suggests greater use of antimicrobials in intensive production. By contrast to extensive or smaller-scale modes of animal production, intensive modes of production rely on high stocking densities and have generated concerns over non-therapeutic use of antimicrobials. Recognizing who controls the inputs of non-therapeutic antimicrobials in vertically integrated livestock or aquaculture production systems though can be key to designing effective policy interventions.

In tackling this global challenge of drug resistance, some regions and countries of the world may contribute disproportionately to the growth in consumption of antimicrobials in food animal production. The OECD analysis projects that China and the United States will account for 40 percent of global antimicrobial consumption in food animal production by 2030. Intensive production also lends itself to geographical concentration. The growth in industrial pig and poultry production will give rise to hotspots of increased antimicrobial consumption, particularly in Asia. By analyzing trade patterns, it can be seen that some countries are more reliant on the import and export of livestock and poultry products. With the flow of such trade also comes the risk of transporting drug-resistant pathogens across borders.

The primary goal of a research agenda focused on economic analysis is to estimate the human disease burden attributable to antimicrobial use in food animals. When considered on a global scale, infrastructure enhancements are needed to drive data collection and surveillance systems. In developing countries, investments in human and physical resources may be required before data collection will be possible. The secondary goal of a research agenda is to identify what costs and benefits are associated with antimicrobial drug use in food animal production. Better empirical data are needed on the costs and benefits of antimicrobial uses under varying production practices, food animal species, and environment. A third goal of a research agenda is a broader market analysis for antimicrobial drug use in the industry. In addition, such analysis should consider price fluctuations and potential cost savings that affect consumer demand and access to food animal products. Externalities from antimicrobial uses (in the form of not just human health effects, but ecosystem impacts) should be considered, and have yet to be well measured. A final goal of a research agenda is the ethical evaluation of the distribution of costs and benefits of antimicrobial drug use in food animal production across stakeholder groups. To ensure that benefits and risks are equitably distributed, such evaluation could occur on the global scale or within country, considering unique subpopulations that are placed at disproportionate economic or disease risk.

Prioritizing the research agenda can begin with existing data and projections, but can be refined as data gaps are surmounted. With stakeholder input, this work needs to be accompanied by assessing the feasibility of collecting such data, both in the near term and over the longer term. To provide credible evidence for policymakers, such research must be conducted independent of financial conflict of interest.

We also recommend consideration of alternative strategies less reliant on these data gaps for implementation and monitoring, including strategies developed within a larger ethical framework that considers issues of sustainability, resilience, local accountability, and food security. A systems thinking perspective would consider interventions to reduce the demand for meat, to increase the reliance on plant-based proteins, and to shift from industrial food animal production to more sustainable agricultural practices.

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I.

Introduction

Antimicrobial resistance not only poses challenges to the healthcare delivery system, but also negatively impacts public health through the food system. The use of antimicrobial drugs plays an important role in treating diseased animals, but their use for broader purposes in the food production system undermines efforts to curb antimicrobial resistance. Non-therapeutic antimicrobial use, particularly the use of antimicrobials for production purposes (i.e. growth promotion) or for prophylaxis, has generated significant concern due to growing evidence of its contribution to antimicrobial resistance. The administration of antimicrobials for non-therapeutic use has largely been driven by perceived economic benefits, including greater feed efficiency and growth, decreased time to market as well as lower mortality and morbidity of food animals.

This briefing note builds upon previously completed literature reviews and provides an overview of the current literature on costs associated with antimicrobial use and transitioning to alternative modes of production across livestock sectors and countries. The report also offers a preliminary assessment of what data gaps exist, what data elements might be more pivotal for policymaking and economic decision making, and how these gaps might be filled. Several key components, from defining critically important antimicrobials to trade patterns, would factor into any systems analysis. Finally, a process for developing a research agenda to evaluate costs versus benefits of antimicrobial use restrictions within a more comprehensive systems framework is described in order to inform future policy efforts going forward.

II.

Antimicrobial Use in Food Animal Production

Definitions and uses of antimicrobials in food animal production. Antimicrobial administration occurs across the spectrum of food-producing animals, including porcine, avian (layers and broilers), ruminants (such as dairy, beef and sheep) and aquatic species. These drugs are administered for a variety of purposes in the production setting, including both therapeutic and non-therapeutic uses. In this report, we define therapeutic as any use where the following conditions have been met: identification of a diseased animal, selection of an antimicrobial appropriate for a particular livestock or aquatic species at a sufficient dose to suppress or kill the target bacterial agent, and a time-limited duration for treatment of a diseased animal or control of the spread of the pathogen to the rest of the flock or herd. The presence of disease within food animals should be determined by veterinarian or laboratory diagnosis. We acknowledge though that resources to confirm such a diagnosis by these means may not be available across all settings. In this briefing note, non-therapeutic refers to uses that do not meet these conditions since the antimicrobial would be administered in the absence of the confirmed diagnosis of a diseased animal. Importantly, the adopted WHO Global Action Plan on Antimicrobial Resistance calls for "phasing out of use of antibiotics for animal growth promotion and crop protection in the absence of risk analysis" and "reduction in nontherapeutic use of antimicrobial medicines in animal health".[1]

Quantity of antimicrobials in agriculture. While the quantity of antimicrobials used in agriculture globally is not known precisely, the amount used for food animal production is significant compared to human use. Based on 2012 data from the U.S. Food and Drug Administration, 80 percent of antimicrobials, by weight, are sold or distributed for use in animals.[2] An analysis conducted for the Organization for Economic Cooperation and Development (OECD) estimates that antimicrobials used in food animal production will grow globally from 63,000 tonnes in 2010 to 106,000 tonnes by 2030—an increase of 67 percent.[3] This rising tide of antimicrobial use is propelled, in part, by the growing demand for animal protein and anticipated increases in industrial food animal production. By this, we define industrial food animal production (IFAP) as involving "high throughput animal husbandry, in which thousands of animals of one breed and for one purpose (i.e., pigs, layer hens, broiler chickens, ducks, turkeys, beef or dairy cattle, finfish, or crustacea) are raised with short-generation intervals at single sites under highly controlled conditions, often in confined housing, with defined feeds replacing access to forage crops."[4]

The OECD study attributes one-third of the global increase in antimicrobial consumption to the shift towards intensive farming systems and two-thirds as a result of the larger number of food animals in production. Annual meat consumption is projected to rise both in industrialized and developing countries. Those in industrialized countries already consume three times more meat than those in developing countries, and from the late 1990s to 2030, increases in the level of meat consumption are projected in industrialized (from 88 to 100 kg per person) and developing countries (from 25.5 to 37 kg).[5] This study is, however, limited to terrestrial animals and excludes fish and other aquatic species.

Antimicrobial use as a driver of drug resistance. Use of antimicrobials drives selection for resistance among bacterial pathogens. Demonstrating the linkage between the use of non-therapeutic antimicrobials and the transmission of antimicrobial-resistant bacteria and associated infections from food animals to humans is multi-step and challenging due in part to restrictions on access to IFAP facilities to sample animal herds and workers.[6] Despite the challenges involved, multiple studies show an association between the use of antimicrobials in animals and the prevalence of antimicrobial-associated bacteria in animals and humans.[7,8] Various expert groups, from a Joint FAO/OIE/WHO Expert Workshop to the United Kingdom (U.K.) government's Swann Committee and the U.S. Food and Drug Administration Task Force, have documented the risk of cross-species transmission of drug-resistant pathogens.[9,10] As the U.K. Review on Antimicrobial Resistance also has shown, the preponderance of published papers offer evidence that support limiting the use of antimicrobials in agriculture.[11]

The transmission of drug-resistant pathogens does not recognize geographic or political borders. Since its first documented case in 2008, New Delhi metallo-ß-lactamase—which mediates resistance to carbapenems, a mainstay in human treatment of bacterial infections—has spread to 40 countries.[12] As the spread of strains encoding for metallo-ß-lactamases demonstrate, bacteria resistant to nearly all classes of antimicrobials have compelled clinicians to bring back old antimicrobials, once removed from use because of toxicity concerns, as last-line defenses. Colistin, a polymyxin drug, is a case in point. For decades, veterinarians have used the drug for both prophylactic and treatment purposes. Typically administered orally, in feed or drinking water, colistin is used to treat groups of livestock suffering from gastrointestinal infections due to Gram-negative bacteria. In Europe, polymyxins has been the fifth most widely sold group of antimicrobials (4.5 percent) though there are alternatives—depending on local resistance patterns—for its use in veterinary medicine.[13] The drug's toxicity to the nervous system and kidneys once limited colistin to topical and ophthalmic use in humans, but with the emergence of multi-drug resistant Gram-negative bacterial infections resistant to all other antimicrobials, colistin has been returned to service. Recent evidence of *colistin-resistant E. coli* and *Klebsiella pneumoniae* in swine and humans in China and other countries have raised serious human health concerns about antimicrobial use practices in food animal production.[14,15]

Studies have suggested that the productivity gains of non-therapeutic antimicrobials, particularly for production-purposes, vary widely.[16] Measures such as average daily growth and feed efficiency also differ depending on the production conditions and practices of operations. For instance, an observational study following the 1986 ban on growth-promoting antimicrobials in Sweden found a greater negative effect for those production facilities with lower sanitary and hygienic conditions.[17] The size of the operation also has played a role on how antimicrobials are used as larger operations in the United States have been found to be more likely to use antimicrobials to accelerate growth and prevent disease.[18] Nevertheless, in countries such as Denmark, Sweden, and Netherlands, which are among the world's largest exporters of food animal products with largely intensive operations, bans on growth-promoting antimicrobials have not adversely affected productivity over time – in fact, productivity levels have been maintained or been increased.[17,19,20] This has been attributed to changes in production practices and use of antimicrobial alternatives that have decreased the need for such non-therapeutic uses.

III.

Overview of Economic Costing Analyses of Use of non-theraputic Antimicrobials

Studies to examine the economic impact of withdrawing antimicrobials for growth promotion or feed efficiency across livestock and aquaculture sectors have primarily been limited to countries within Europe and the United States. Across these studies, researchers have typically proceeded by first characterizing the immediate economic impact of phasing out the use of production-purpose antimicrobials at the animal-level. Some studies have considered how adjustments in production processes at the animal and farm level can mitigate or offset the immediate economic costs. Finally, other studies have also estimated how markets for agricultural products will respond to the described changes.[6] Across all three levels, these studies have quantified the costs and benefits of switching to a production arrangement without non-therapeutic use of antimicrobials for producers. These economic effects will vary depending on the livestock sector and type of production system, could be either the farmer raising the animals or the integrator who typically owns the animals and contracts farmers to raise them. At the market level, researchers have also quantified how changes in market prices of food animal products will share the burden of any costs between consumers and producers.

At the animal level, the immediate cost of withdrawing non-therapeutic antimicrobials, without adjustments in production processes may include decreases in feed efficiency, growth, survival, and number of animals born per litter as well as higher variability of the end product.[16] On the other hand, benefits at the animal level of restricting the use of such drugs might include preservation of antimicrobial efficacy to treat animals when needed.[16]

Looking more broadly at the farm level, these costs can be mitigated by investing into alternative production methods. These include alternative methods to maintain live weight and feed efficiency through increased feed or the use of additives, the use of vaccines for disease prevention, if available for the target disease. Furthermore, producers may find increased near-term costs to reduce the density of animals in production facilities and to improve sanitary and hygienic conditions that would decrease the selective pressure to use antimicrobials for production or prophylactic purposes. These costs, however, might be incurred by the producer only in the short-term. Over the longer term, these improvements in production facilities will translate into better animal welfare and health, thereby reducing the need for non-therapeutic use of antimicrobials and veterinarian costs. However, the initial investment for these improvements may impose a considerable burden on smaller producers in low- and middle-income countries.

Reductions in the use of non-therapeutic antimicrobials may also have potential economic effects in the market for agricultural products. It is possible that countries with tighter regulations on use might become less competitive in meat-export markets if such restrictions increase production costs.[6] Additionally, if producers increased livestock feed to maintain live weight and to substitute for the use of antimicrobials for growth promotion, this might affect other input markets such as grain.[21] These increased costs resulting from changes in production practices might reduce the food animal supply, which would in turn, lead to increases in the price of the end product, implying that consumers are sharing the burden of increased costs with producers. In response, there may also be a quantity adjustment in that consumers reduce consumption. However, at the same time, better information and increased awareness of antimicrobial use in food animal production might contribute to greater consumer demand for meat and fish products raised without production-purpose therapies. Consumers not only might be willing to absorb the resulting price increases, but these shifts in consumer demand could also affect production practices as the demand for sourcing meat raised without the routine use of antimicrobials rises.[22]

Using a structured search of the literature, 24 studies providing economic costing data on production-purpose and prophylactic antimicrobials were identified. Only studies that included costing figures of economic effects were reviewed. This briefing note focuses on published literature, including those in peer-reviewed journals or analyses conducted by governmental or intergovernmental agencies, but excluded review of gray literature or non-English literature. Using key search terms in PubMed, Web of Science, Ag Econ Search, and Google Scholar, all available studies matching the criteria as outlined in Appendix I were reviewed. Additional sources of review included reports from the U.S. Department of Agriculture Economic Research Service (USDA/ERS), the National Academy of Sciences, and the World Health Organization (WHO). Studies identified were limited to United States and European countries and largely focused on the effect of such regulations on intensive food animal production operations. The units of analysis of these studies were at the animal, farm and market levels. All costing figures described below are reported in 2015 $USD.

A.
Economic effects of production-purpose antimicrobials at the animal level and farm level

To estimate the economic effects of production-purpose antimicrobial use at the animal and farm levels, researchers have quantified productivity effects based on experimental and observational studies (Appendix II). Across all livestock sectors, these studies have shown wide variation on the economic effects of imposing regulations on non-therapeutic antimicrobials at both the animal and farm levels. This is largely due to the range of productivity estimates used to calculate the costs to the producer, which are related to factors such as the study design (control experimental vs. observational vs. model estimates) and the measures (feed conversion efficiency, mortality, growth rate, time to market, and live weight) selected.

Several scientific studies from the late 1980s and 1990s provide data on the improvements in feed efficiency, mortality, and sort loss in hogs (reduction in price for meat that does not meet size or carcass quality definitions) in the United States due to growth promoters. From these studies, researchers estimated that producers benefited by approximately $3.66 per animal when administered growth promoting antimicrobials.[23] Using survey data from 1990 and 1995, another study estimated that the use of growth promoting antimicrobials increased profits by $0.76 per pig marketed.[24] This use of growth promoters was also estimated to contribute to 9 percent of net returns of typical Midwestern U.S. operations. The same authors conducted a subsequent study using 2000 National Animal Health Monitoring Survey (NAHMS) data to quantify the dollar contribution that production-purpose antimicrobials have on hog weight and reductions in the variability of the animal. They found that removal of antimicrobial growth-promoters would decrease profit for individual pig production operations by $1699 due to the changes in the live weight and that the variability in animal size was a significant factor affecting productivity.[25] An updated study using the same 2000 NAHMS dataset from the same authors found that the loss in profit due to changes in the variation of average daily gain, feed conversion ratio, mortality rate, and stunted rate are estimated to be $1748 per 1,020 head barn, or $1.71 per animal.[26]

A 2009 study of U.S. swine production modeled the impact of a ban on antimicrobial growth promoters across differently sized operations.[27] The study assumed that economies of scale were realized by larger operations and that these operations were lower cost. In this simulation study, the removal of antimicrobial growth promoters did not sufficiently give a productivity advantage to smaller scale operations over large-scale operations. The model here assumed that there would not be dynamic changes by consumers or producers in response to the ban of antibiotic growth promoters. In this study, the meat product price faced by consumers was held constant, and growers did not alter practices to ensure similar productivity levels by adapting to these bans.

Over time, larger scale efforts at reducing antimicrobial use in livestock production have taken place. In 2002, a WHO evaluation panel conducted a study on the economic impacts of the ban in Denmark on antimicrobial growth promoters on both the pig and poultry industries.[28] They estimated that the Danish system had experienced a net increase in costs to the producer as a result of the ban of €1.27 per pig ($1.45 USD) and €0 for poultry ($0 USD). Smaller costs that could be measured include excess mortality, an increased number of feeding days to achieve a target live weight, increased use of therapeutic antimicrobials, and increased labor. The panel was unable, however, to take into account larger costs such as modifications to production system that are more difficult to measure. Nevertheless, the WHO evaluation panel found that in the period following implementation of the ban on antimicrobial growth promoters, the overall volume of pork production continued to increase.[28] Additionally, although there was a rise in the use of therapeutic antimicrobials immediately following the ban, there was an overall decrease in antimicrobial use.

Estimates of economic impacts of phasing out antimicrobials also vary across different livestock sectors. A 2007 study that used industry data on the productivity effects of antimicrobial growth promoters in poultry found that a cost savings of $0.0093 per chick or 0.45 percent of the total cost per animal.[29] This small figure might suggest that the cost of using growth promoters is greater than the benefits of lower mortality rates and greater feed efficiency. This value, however, is based on the authors valuing broiler poultry at the fee paid to the grower at $0.05 per pound rather than at the fee paid to the integrator, which is higher ranging $0.40-$0.50 per pound.[6]

Using the U.S. 2006 National Agricultural Resource Management Survey (ARMS), another study found that growers of broilers who did not use production-purpose antimicrobials suffer no loss in productivity. These growers applied livestock practices such as testing poultry flocks more routinely for pathogens, providing better sanitation, and having newer buildings.[30] These growers saw no difference in productivity: they received higher contract fees, but also likely saw higher labor and capital costs to maintain the sanitation requirements under Hazard Analysis Critical Control Point (HACCP) plans. Growers who forgo the use of production-purpose antimicrobials saw no significant difference in feed-conversion rates. This suggests that growers could adapt to restrictions on non-therapeutic use without declines in production.

These costs differ depending on the livestock involved. Compared to the pig and poultry industries, much less research has been conducted on economic effects of phasing out the use of production-purpose antimicrobials in beef cattle at the farm level. In another 2002 study by the USDA/ERS, researchers modeled the impact of a complete ban on non-therapeutic antimicrobials in beef in terms of the changes in cost of feed and space requirements per animal. This model found that such a ban would incur an additional $6.25 per animal and $0.06 in average cost per pound of weight gain.[31] A 2007 study modeled the effects of discontinuing antimicrobials for production purposes in beef using data from prior experimental studies from the 1980s and 1990s. The model showed that a ban on such therapy would lead to a rise of $11.06 per animal in production costs in stocker operations and a rise of $6.77 per animal in beef feedlots.[32] Regardless, the percentage change in costs of production due to a ban on subtherapeutic antimicrobials was found to be less than 1 percent [32], indicating that the overall increase in costs to the producer is nominal compared to the overall cost.

Across all livestock sectors, these studies have shown wide variation in the economic effects of imposing regulations on production-purpose antimicrobials at both the animal and farm levels. These economic analyses rely on controlled experimental studies and simulation models. Such variation in economic effects is due to the range of productivity estimates used to calculate the costs to the producer. Many of these analyses also do not assume that producers will change their production practices to offset the costs due to loss in growth, feed efficiency, and other productivity measures. In fact, observational studies suggest that the increased costs as a result of production-purpose antimicrobials might be overcome by changes to production practices such as improved sanitary conditions that decrease animal density. Moreover, application of these economic effects to other countries, particularly low- and middle-income countries, as well as to other production systems is unclear as costing analyses and much of the evidence on the productivity effects have largely been found in livestock sectors in the United States or European countries as well as within intensive operations.

B.
Economic effects of production-purpose antimicrobials at the market level

Studies at the animal and farm levels often fail to examine market-level impacts of a ban on production-purpose antimicrobials. This is critical, since an increase in market prices of animal food products raised without antimicrobials implies that consumers are sharing the burden of adjustment with producers. Researchers, however, have attempted to estimate these impacts on market supply and price across livestock sectors in the United States (Appendix III). For these analyses, researchers employ industry supply and demand models to predict how such bans might affect the supply and price of meat products across livestock sectors.

Researchers began to examine these economic effects as far back as the 1970s when U.S. policymakers were initially considering regulations on production-purpose antimicrobials. Some scenarios involved the use of non-therapeutic antimicrobials to increase feed efficiency. Other studies assumed that without use of growth promoters, animals would either need to be fed for longer periods or with greater amounts of feed to bring the animal to market within the same amount of time. Due to these assumptions, researchers found a wide variation of market effects across different scenarios. An earlier study found that depending on the magnitude of productivity effects, discontinuing non-therapeutic antimicrobials is predicted to lead to a wide range of changes in production costs ranging from a decrease of $33.6 million to an increase of $23.4 million.[33] This same study also estimated that the retail price of broiler poultry would also vary from $0.17 to $12.92 per pound, depending on the assumptions made.[33] Modeling a complete ban on growth promoters decreased the quantity produced by 2.244 percent for poultry and 3.184 percent for turkey and increased the market price by 22.48 percent and 13.71 percent, respectively.[33] In a 1975 study by Gilliam and Martin the market price per pound increased by $0.089 for beef and $0.31 for swine when antimicrobial feed additives were discontinued.[34] In this study, researchers also assumed no changes in production practices in response to a ban and perfectly inelastic consumer demand for meat.

Using productivity effect data from an expert committee rather than experimental data, the U.S. National Research Council found negligible decreases in per capita costs of chicken, beef, and pork meat per year ($0.02-$0.08).[35] However, this study has come under critique. The USDA notes that "the NRC assumes no changes in prices or quantities due to changes in subtherapeutic antibiotic use, basically ignoring economic theory."[6]

However, the results were different when the market price for meat produced without non-therapeutic use of antibiotics was allowed to rise. In 1976, Dworkin in 1976 used productivity effect data from the 1960s and modeled four different scenarios of the market response to a ban on tetracyclines. He found that the production costs per animal in the beef and pig sector would decline, as a result of savings when animals were not fed alternative medicated feeds and when they were fed for the same amount of time before the ban.[36] Although this study predicted that the quantity of animals produced would decrease, it also estimated that market prices would increase, thus contributing to a rise in revenue.

Like the Dworkin study, the USDA conducted a study in 1978 that also contrasted near-term and medium-term impacts of a ban on subtherapeutic antibiotics.[37] In this study, the USDA modeled the market effects of a ban on selected antimicrobials and found that the increases in market price for hogs, broilers, turkey, and beef and the decreases in quantity produced were greatest in the first year after implementation of the ban, but these changes return to pre-ban levels by the fifth year. This study also examined the effect of such a regulation on other input markets such as grain. Assuming that livestock will require additional feed as a result of phasing out growth promoters and lowered efficiency, more grain will be required, thereby decreasing its unit price.

In 2001, an Iowa State University group conducted econometric simulation analyses of the market impact over time of a ban on production-purpose antimicrobials in swine production.[38] Despite the modeled ban resulted in a decrease in quantity produced by hog farmers, the average producer would be unlikely to experience "financial disaster" as a result of the ban. This is because pork prices would also rise and allow for profits even in the short-term. As studies in the literature began to reflect changes in elasticity of demand for food animals produced without non-therapeutic use of antibiotics, producers are able to remain profitable. The same authors applied productivity data from the Swedish ban to the U.S. market. They found similar trends for production costs and profits in the swine sector. The regulation had the greatest impact in the first year ($8.61 dollars per animal increase in production costs and $5.93 per animal decrease in profits), but then returned to almost pre-ban levels by the tenth year.[39]

Following a ban on non-therapeutic antibiotics, modeling studies show near-term increases in production costs and lower profits, but returns to pre-ban profitability over time. Using data from the 1998 ban on growth promoters in Denmark, modeling by a WHO international review panel found that the policy impacted differently the swine and poultry sectors.[28] The model projected that production costs increased, resulting in a decrease in the quantity produced in the swine sector by 1.4 percent annually and an increase in the poultry sector by 0.4 percent annually. The study investigators attribute the increase in poultry production to the fact that poultry and pig production compete for inputs and consumption. As a result, lower pig production actually benefits poultry consumption. The model also estimates that the ban on antibiotic growth promoters would result in a reduction of 0.03 percent in real Gross Domestic Product in Denmark. Importantly though, the model did not consider factors that could have offset such losses, such as changes in consumer demand or export markets for meat products produced without non-therapeutic use of antibiotics. In fact, the report notes that pig prices increased following the Danish withdrawal of growth promoters, and this might have mitigated the transition costs of the Danish swine industry in adapting to the change.

Instead of assuming that consumer demand for meat products is perfectly inelastic as in the studies described above, other studies have modeled that consumers would be willing to pay a higher price for meat perceived to be safer.[40] Using supply and demand data over 30 years and further assuming that such a regulation would decrease overall supply of pork by 4 percent, they predicted that the price for pork would rise by 3.2 percent and quantity produced of pork would be reduced by 2.8 percent. Thus, as consumer awareness around use of production-purpose antimicrobials and their demand for meat products raised without non-therapeutic therapies increase, these shifts may lessen the economic effects of the ban on market price and supply.

Matthews in 2002 analyzed the impact of a complete ban on production-purpose antimicrobials in the beef sector. [31] Assuming robust gains in growth rate (6 percent) and feed efficiency (4 percent) from using non-therapeutic antimicrobials, this study projected that a ban would result in a 9 percent decrease in beef cattle production and a 3 percent increase in price. In study after study, we see how sensitive projections are to underlying assumptions, but also that the growth promotion effects of antimicrobials can be offset in part by either changes in production practices or consumer price increases of the end product.

In 2015, the USDA/ERS published a comprehensive analysis using data from ARMS and NAHMS to examine how regulations on the use of non-therapeutic antimicrobials affect market-level outcomes including price and quantity across broiler, swine, beef, and dairy cattle.[6] The researchers assumed that non-therapeutic antimicrobial use would increase productivity by 1 to 3 percent. This USDA market model demonstrated that a 1 to 3 percent increase in the cost of production as a result of phasing out non-therapeutic antimicrobials would raise wholesale prices by 1 percent and lower output by less than 1 percent. The study also suggests differences between producers who had already phased out use of production-purpose antimicrobials and those who had not. Those that had phased out the use of antimicrobials before the ban were projected to increase production in anticipation of higher consumer prices. As their production costs would remain unchanged as a result of the ban, their total revenues would also increase.

The studies described above clearly show that economic impacts at the market level will vary based on the estimated productivity effects of non-therapeutic antimicrobials. The economic effects at the market level over time will also vary based on the response of the production system and consumer demand. In fact, observational studies indicate that the costs of such restrictions could be largely offset once producers adopt certain production practices such as improvement in sanitary and hygienic conditions, adoption of alternatives to antimicrobials such as feed additives or vaccines, and decreased density of animals in production facilities.

It is critical to consider the limitations associated with looking exclusively to costing studies for animal agricultural antimicrobial use as the basis for decision-making purposes. These studies do not incorporate important externalities linked to the decision to use these drugs for non-therapeutic purposes. As with any use of antimicrobial drugs, the risk of development and propagation of resistant organisms is directly related to the rate of use. Non-therapeutic antimicrobials are administered at sub-therapeutic doses, often not applied for time-limited periods coinciding with disease treatment, and given, sometimes with inconsistent dosing, through feed and water, typically without the identification of a likely bacterial agent (since these uses are not tied to a specific disease or disease risk). As a result, these contribute to the likely emergence of existing and new multidrug-resistant pathogens from animal production facilities, posing risks of transmission to humans. These transmissions, which can occur through environmental pathways and the diet, can cause serious infections in humans that, when compared with non-resistant infections, impose greater economic burden and are more likely to be fatal.

To date, barriers exist to the quantification of the societal burden of resistant infections that originate from the non-therapeutic use of antimicrobials in food animal production. To start, a paucity of use data complicates relating resistance patterns observed in bacteria to patterns of administration. Furthermore, collection of surveillance or clinical isolates for isolates to be collected from food animal production facilities, food animals, or the environment surrounding food animal production facilities for genetic or other comparison with isolates from human clinical infections does not occur frequently. Without the routine collection and archiving of such bacteria, attribution of human infections to food animal sources will prove incredibly challenging. As a result, the externalized cost of these human infections is difficult to quantify, and thus has not to our knowledge been included in prior benefit-cost analyses of the non-therapeutic use of these drugs in food animal production.

Moreover, it is uncommon for isolates to be collected from farms, farm animals, or the farm environment for purposes of comparison with isolates from clinical infections. Without the routine collection and archiving of such bacteria, attribution of infections to farm sources will prove incredibly challenging. As a result, the externalized cost of these infections cannot be quantified, and thus cannot be included in a benefit-cost analysis regarding the non-therapeutic use of these drugs.

IV.

Alternatives to Non-Therapeutic Antimicrobial Use

Alternatives to non-therapeutic antimicrobial use range from changing production practices to using substitutes. Changes in production practice that would reduce the need for non-therapeutic antimicrobials might include altering the weaning period, lengthening the feeding time, or improving sanitary and hygienic conditions. Substitutes for these therapies include vaccines, micronutrients, and other non-antimicrobial feed fortificants (i.e. fish oils). The literature review of costing studies at the animal, farm and market levels provides limited data on the costs of switching to such alternatives to non-therapeutic use of antimicrobials.

Both agricultural researchers and food animal producers have attempted substitution of alternative non-antimicrobial strategies to replace production uses of antimicrobials in food-producing animals, with varying economic costs. By replacing the need for antimicrobials for non-therapeutic use, alternative production approaches should help decrease the antimicrobial selective pressure of such uses of these drugs.

At the most basic level, when antimicrobial drugs are used for production purposes, the default substitution is to employ the strategy used prior to the introduction of these uses for growth promotion and feed efficiency: increasing quantity of feed and/or time in production to achieve the same weight gain. The disadvantage to this approach—and therefore the primary critique—is that doing so relaxes the standardization employed by industry as part of the vertically-coordinated industrial model. In other words, both the process and the built environment designed to support that process require uniform inputs in terms of time and weight of the animal commodity; the costs of changing the required inputs are difficult to estimate and likely will vary across food animal sectors. Some of these costs could be offset through the continued practice of selective breeding, placing emphasis on intrinsic weight gain without antimicrobial inputs, on animal hardiness and health parameters, and on conformation.

Increasingly, attention has been paid to identifying and using other additives, drugs or biologics that replace or reduce antimicrobial inputs to improve or maintain feed efficiency and prevent disease, such as vaccines, exogenous enzymes, organic acids, fish oils, flavor enhancers, prebiotics, probiotics, and plant extracts, and/or vitamins and other nutrients.[41] The relative costs or return on investment, and thus the economic efficiency for such substitutions, have not yet been widely examined. One review estimated a positive return-on-investment of 3-25 €/ton[9] for such uses;

however, this was not compared to the return on investment for antimicrobial uses.[42] In addition, the economics and feasibility for use of vaccination as a substitute for infection control are difficult to estimate, depending in large part on the animal sector and specific pathogen or disease condition under consideration, and some reports indicate that the benefits of using these may vary widely.[43]

One of the more commonly considered strategies, drawing from the Danish experience, is improvement in hygiene and reduction in stress through changes to the production style, stocking density, and built environment.[44] Such changes to production practices include cleaning facilities, improving ventilation and switching from gestation crates to pen system for swine. While such changes may require initial high capital investment costs and moderate resource inputs over time, they are among the most effective of the alternative strategies. Specifically, stress and poor hygiene contribute to disease susceptibility, and disease can lead to increased uses of antimicrobial inputs for prevention or control uses.[35] So by changing the environment and decreasing the stocking density, producers can reduce the stress and disease transmission as well as improve control of temperature, humidity and hygiene in ways that benefit animal health.

Alternatively, another strategy to reduce overall volume or mass of antimicrobials used in food-producing animals would be to reduce the industry itself in favor of production of plant-based protein sources that do not depend on antimicrobial inputs.

V.

Data Gaps in Capturing Costs of Curbing Non-Therapeutic Antimicrobial Use

Reviewing comprehensively or systematically the availability of country-level data on antimicrobials, drug-resistant pathogens or livestock production practices is beyond the scope of this briefing note. However, even in industrialized countries, existing datasets fall short of providing a complete picture as a result of their sampling design (representativeness, consistency of livestock sampled), confidentiality restrictions (failure to make publicly transparent the indication of antimicrobial use, farm-level usage of antimicrobials), and other challenges. At the country level, some data collection efforts, such as the Danish Yellow Card system, offer examples of how a country might capture which farm operations are using antimicrobials and share prescription-level data to show the degree of use across different livestock operations. At the global level, however, UN COMTRADE data do not allow the tracking of antimicrobials destined for human or veterinary use from one country to another.

Cost comparison between Denmark and the U.S. suggests that the two countries had similar per-capita costs for national surveillance spending on antimicrobial resistance in food production systems—$8 in Denmark for AMR surveillance as well as other agricultural spending, and $6 per capita in the U.S. annually for AMR surveillance alone.[45] The authors concluded that key components to the relatively greater success of the surveillance system in Denmark were attributed to greater industry involvement in AMR control efforts, greater standardization of data collection in Denmark, and better data transparency.

The shortcomings of existing data include gaps in surveillance data, costing data, and data on production practices and characteristics. Economic studies from high-income settings such as the United States and Europe must be complemented by studies conducted in resource-limited settings, and local costing data for existing and alternative production practices would be important to capture. Differing across country context, the degree of intensive livestock production and the vertical coordination of such production practices also significantly influence where the costs fall upon growers, processors or integrators. At the same time, such data might inform the best approach to implementing changes, but need not delay efforts to remove non-therapeutic use of antimicrobials in agriculture.

Surveillance data would capture how antimicrobials are used and how drug resistance manifest at different points in the food animal value chain. Characterizing how and to what degree specific antimicrobial agents are used in food animal production--by animal species, indication, and route of administration—would be key. These patterns of use should be coupled with surveillance of antimicrobial resistance in food animals and humans who raise food animals and humans living in regions with a high density of food animal production. Such monitoring could improve understanding of the contribution of the various routes of exposure to food animal and human disease risk. Most people are exposed through contaminated poultry, meat, fish and dairy products. Following the path of food commodities, surveillance can detect drug-resistant pathogens in food animals, in the slaughterhouses, and in retail outlets as well as points of trade. Such findings might help prioritize where surveillance might be most cost-effectively implemented. Another route of transmission of drug-resistant pathogens is from the food animals to the workers raising food animals and individuals living in the surrounding communities. Additional surveillance is needed that focuses on areas of high-density food-animal production.

Central to this analysis, costing data involves factors at the level of the animal, farm and market. These component costs vary by setting. Animal-level factors include feed efficiency (the feed required to achieve a certain weight gain), mortality and morbidity among the livestock or aquaculture, and the average daily gain in weight among other concerns. Farm-level factors would address component costs like veterinary costs, the cost of antimicrobials used, feed costs, and labor costs, whereas market-level factors could address the costing of the quantity of food animal products and the revenue from their sales at different points in the food value chain.

Data may have to be collected at several points in the value chain, both to establish the validity of measures and sometimes to develop proxies where routine data collection of certain data elements will not be possible. For example, tracking the use of antimicrobials in food animal production would benefit from the collection of 1) sales data of drugs for agricultural use from pharmaceutical companies; 2) prescription data from veterinarians that would show the indication, dose, route of administration, and specific livestock and aquaculture sectors; and 3) use data from producers indicating the amount of antimicrobials used across livestock and aquaculture sectors as well as by indication. Depending on local circumstances, some data collection may not be feasible. For example, without veterinary oversight, prescription data would not be available.

Across the spectrum of intensive to extensive agriculture, costing data will differ. At the country level, data on production practices and characteristics would help such analyses to go beyond the intensive-extensive dichotomy of food animal production systems, especially as such a binary characterization of production practices might not exist in many countries nor correlate with the level of antimicrobial usage. Instead, data on the structure of food animal production should make clear the level of vertical coordination, adherence to specific sanitary and hygienic standards, the structure of the facilities including the level of animal density, and the localization of facilities to address biosecurity concerns.

Food animal products and drug-resistant pathogens readily cross borders. Some countries have a disproportionate share of the import or export market for these commodities, and such trade patterns can inform where the global community might focus its efforts. However, on the export side, tracking not only the sourcing of food animal products, but also the flow of antimicrobials use in agriculture may be helpful. At the global level, changes in the UN COMTRADE data coding should allow for tracking of antimicrobials destined for veterinary as opposed to human uses.

Significant data gaps on antimicrobial use in aquaculture mirror the overall dearth of economic costing literature in this area. However, the contrast between aquaculture practices in Norway and Chile is noteworthy (see **Antimicrobial Use in Aquaculture: A Case Study of Chile and Norway**). There are, however, a handful of studies on the economic costs and benefits of fish vaccination. In one study, authors compared the productivity of unvaccinated to vaccinated populations of Atlantic salmon and sea bass.[46] Such data can be incorporated into decision-making frameworks to help businesses and industries determine the cost-effectiveness of introducing vaccines. This study acknowledges that a benefit of vaccination is a reduction in the use of antimicrobial therapies, but do not characterize the economic benefits specifically in terms of types of antimicrobials or contribution to antimicrobial resistance.

Given limited resources to collect such data, a strategic approach must be undertaken to identify the most important data gaps to address first. Further work needs to be conducted to prioritize such data collection, so that data would inform effective policymaking.

Numerous considerations exist that call into question the non-therapeutic use of antimicrobials in animal agriculture. Depending on the country in question, however, it may be strategic to target messaging around specific policy levers that are most likely to resonate with the interests or priorities of policy makers. In the contexts of some countries, the economic costing of curbing non-therapeutic use of antimicrobials would be important to gauge in order to secure policymaker support of such measures. Accordingly, data collection efforts can be tailored to these specific policymaker interests; in particular, opportunities may exist in low- and middle-income countries where industrialized methods may be increasingly employed. As antimicrobials may be newly introduced into production settings in new countries, well-designed data collection protocols can be implemented. Given what has been observed in countries where industrialization is currently the dominant model of production, these studies may likely fail to demonstrate a meaningful economic return associated with non-therapeutic use.

Antimicrobial use in aquaculture: A case study of Chile and Norway

Infectious diseases remain a constant challenge for the aquaculture industry. Producers of farmed aquatic animal species treat bacteria and other microorganisms with a variety of veterinary therapies including, antimicrobials, disinfectants, pesticides, probiotics, and vaccines. Use of antimicrobials for growth promotion in aquaculture has been banned in the European Union, but there is evidence that these drugs are used for growth promotion in other parts of the world.[69,70] In addition, a European aquaculture expert reported that it is commonplace to treat an entire population if a handful of animals are diseased.[71] As with other food animal industries, antimicrobial use in aquaculture contributes to the emergence of drug-resistant pathogens on farms, and can spread to workers and through the environment (i.e., water, sediments, effluents) and meat.[72,73]

In the aquaculture sector, antimicrobial use is not routinely tracked nor publicly available in most regions of the world, except for Europe where reporting regulations and a ban on prophylactic uses passed in 2006[66] have been instrumental in reducing antimicrobial use. The best evidence of global antimicrobial use in aquaculture comes from scientific reports, expert surveys, government seafood inspection programs, and limited national and industry reporting. From 2000 to 2008, a seafood inspection program in the European Union found 790 veterinary drug residue violations among 40 exporting countries, including 17 different types of antimicrobials.[74] These food inspection reports provide limited, and alarming, information indicating the global use of antimicrobials in aquaculture is quite significant.

Researchers at the University of Guelph in Canada recently led one of the largest expert surveys on antimicrobial use and resistance in aquaculture with over 600 respondents from 25 countries.[75] Their study found that antimicrobial use and multi-drug resistance were common among the major species groups of seafood. These findings are consistent with results from an earlier review article, which found eight classes of antimicrobials were in use among the top-15 aquaculture producing countries.[76] Global expert surveys and review articles are corroborated by surveys of antimicrobial use conducted among farmers in Bangladesh, China, Nigeria, Thailand, Vietnam and United States for the production of shrimp, tilapia, pangasius, and catfish.[92,93,94] Many of the drug classes reportedly used by farmers are considered critically important to human medicine by the WHO.

Norway and Chile are the world's largest and second largest farmed salmon producers, however, there are dramatic differences in the amount of antimicrobials used in these countries to raise salmon. In 2013, Chile used antimicrobials at a rate of 0.63 kg per metric ton of salmon produced, which was 900 times more than the rate used in Norway. In 2007, the largest global salmon producer used over three and a half times more antimicrobials per ton of salmon raised in their Chilean operation compared to their Norwegian operation.[80] These differences did not happen overnight, and came from a policy reform process in Norway to intentionally reduce antimicrobial use.

Norway was not always a leader in fish antimicrobial use policy. Norwegians pioneered salmon farming in the 1960s and 1970s, and by the 1980s industrial operations were using large amounts of antimicrobials to control bacterial diseases—at comparable rates to present day Chile.[96] Starting in the early 1990s, Norway began introducing policies that favored a reduction in antimicrobial use. Midtlyng and colleagues[82] describe key activities that reduced antimicrobial use including government support for the development of fish vaccines against a key disease (furunculosis), a government-industry initiative to increase vaccination rates by fish farmers, adoption of production practices that reduced disease transfer among age classes on a farm, and spatial planning and reorganization of marine production sites to reduce the spread of diseases between farms. Norway also enacted the Fish Disease Act that requires aquaculture operators to reduce risks related to infectious disease spread and

Table 1. Atlantic salmon production and antimicrobial use in Norway and Chile.

Country, year	**Salmon production** (metric tons)	**Antimicrobials used** (kg)	**Rate of antimicrobial use** (kg antimicrobials/ metric tons salmon)
Norway			
2007	822,000	649	0.0008
2013	1,300,000	972	0.0007
Chile			
2007	331,000	385,600	1.17
2013	895,000	563,200	0.63

Data sources: Burridge et al, 2010[87] provide information about aquatic diseases at their facility upon request by the government.[83]

Chile began to develop its aquaculture industry starting in the 1980s as Norwegian and other investors looked to the country for its favorable growing regions, cheap labor, few environmental regulations, and government support.[84] The farmed salmon industry expanded during two phases of Chilean history, in the 1980s during a period of 'socio-ecological silence' of the Pinochet dictatorship, and in the 1990s when economic expansion was seen as an imperative for the country.[84] As the Chilean salmon industry gained international recognition and became a major global player, the country's regulatory environment and other supporting infrastructure failed to keep pace. These shortcomings were first revealed in a 2007-2010 outbreak of a virus called infectious salmon anemia (ISA), which decimated the Chilean farmed salmon population and resulted in significant economic losses. These failings opened the Chilean salmon industry to outside scrutiny including criticism of the high use of antimicrobials used to combat bacterial diseases. In an interview with Reuters, the head of Chile's aquaculture department said in 2015, "The use of antibiotics is an issue for us... "All companies (in Chile) use antibiotics to a lesser or greater extent." [86] The ISA crisis may be a turning point for the industry,[87] which has included new policies to control diseases and zoning regulations,[81] however, antimicrobial use in 2013 was still at unacceptable levels relative to use in Norway and other salmon producing countries.

Given limited resources to collect such data across countries, a strategic approach must be undertaken to identify the most important data gaps to address first. Further work needs to be conducted to prioritize such data collection, such that data would inform effective policymaking. Three potential targets to help focus efforts to assess the costs of transitioning away from the non-therapeutic use of antimicrobials might include critically important antimicrobials, mode of agricultural production, or geography.

IV.

Conserving Critically Important Antimicrobials

Classifying available antimicrobials can help target high-yield opportunities for improving antimicrobial stewardship. Such steps not only can mitigate patterns of drug resistance seen today, but also anticipate the potential for greater drug resistance tomorrow. Some families of critically important, new antimicrobials might be reserved for human use, and the emergence of resistant pathogens induced by other antimicrobials used might prompt regulatory removal of such drugs from specific veterinary uses. However, co-resistance to multiple classes of antimicrobials makes it imperative to reduce non-therapeutic use of antimicrobials across the board.

The cross-species use of antimicrobials from the same chemical family—working through the same mechanism of action and thereby generating shared patterns of resistance--provides a ready pathway for drug-resistant bacteria to move between animals and humans. Considerable overlap exists among the classes of antimicrobial agents used in human and veterinary medicine.

The focus here is on how these drugs are used in food production, from raising livestock to aquaculture. While antimicrobials are also applied in plant agriculture in places like the United States, controlling bacterial disease in pome fruits like apples and pears likely comprise only a small percentage of overall antimicrobial use (0.5 percent in the U.S.).[47]

Antimicrobial drugs differ in their importance in treating humans and animals. Separate policy processes exist in determining critically important antimicrobials in human and veterinary medicine. Growing out of a joint FAO/OIE/WHO meeting in 2003, WHO began classifying families of antimicrobial drugs as critically important, highly important and important. By 2009, WHO established the Advisory Group on Integrated Surveillance of AMR (AGISAR). This committee laid out two key criteria by which to evaluate the importance of antimicrobials for human clinical use: 1) Criterion 1: An antimicrobial agent which is the sole, or one of limited available therapy, to treat serious human disease; 2) Criterion 2: Antimicrobial agent is used to treat diseases caused by either (a) organisms that may be transmitted to humans from non-human sources or, (b) human diseases caused by organisms that may acquire resistance genes from non-human sources.[59] Applying these two criteria, antimicrobials meeting both Criterion 1 and 2 are classified as critically important for human medicines. Those meeting only one of these criteria are characterized as highly important, and those not meeting either of these criteria fall into the category of important for human medicine. By 2018, WHO has proposed converting the current list of critically important antimicrobials into formal WHO guidelines.[49,50]

Going further than this tiered classification, how might priorities be set among highly important antimicrobials? Again the WHO AGISAR committee has put forward recommendations on factors to consider when evaluating one of the two focusing criteria. For example, to establish the significance of an antimicrobial when few alternatives exist, one can look at the number of people afflicted by treatable disease and the frequency of use across indications in human medicine. Another criterion focuses on the non-human sources of diseases and the risk of transmission to humans. Such an analysis has highlighted fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides as among the highest priority categories of antimicrobials, over which more effective stewardship would be critical.

Dating from the 2nd Joint FAO/WHO/OIE Expert Meeting in Oslo in 2004, OIE has developed a list of critically important antimicrobials for the veterinary sector. This task differs in several key ways from the WHO efforts for human medicine. First, the selection of antimicrobials for veterinary medicine must consider the context of multiple food animal species, not just the single human species. Among those antimicrobials identified as critically important, the preference or need for use in specific species and for specific disease indications may complicate strategies. Secondly, practices vary across different settings. Recognizing the geographic diversity of food animal production, the OIE list begins with replies to a questionnaire sent to the 167 OIE member states.[51] The questionnaire captures four key elements of antimicrobial use: 1) animal species; 2) the disease being treated and the associated pathogen; 3) the antimicrobial drug used, including the type of use and route of administration; and 4) specific rules of usage for the country. In justifying how critical an antimicrobial would be, the questionnaire also requests whether an alternative is available or not. Finally, the process involves several stages, including review by the OIE Collaborating Centre for Veterinary Drugs, the Biological Standards Commission, and the OIE International Committee.

OIE also has two key criteria for rating the importance of antimicrobials:[51] 1) Criterion 1: Response rate to the questionnaire regarding Veterinary Critically Important Antimicrobials (when more than 50 percent rated the antimicrobial class as important, this criterion was met); 2) Criterion 2: Treatment of serious animal disease and availability of alternative antimicrobials (when the drugs were deemed essential for specific infections and without sufficient alternatives, this criterion was met). Similar to the WHO approach, veterinary critically important antimicrobials have to meet both criteria. Veterinary highly important antimicrobials meet either Criterion 1 or 2, and veterinary important antimicrobials meet neither criterion.

Several classes of antimicrobials currently are not used in animal health. These include carbapenems, oxazolidinones, and lipopeptides. Some have called for not using these for food production purposes. Of note, 3rd and 4th generation, not 1st and 2nd generation, cephalosporins, rate as critically important. While the only tetracycline on the WHO critically important list is tigecycline, this class of drugs is widely used in food animal production, and it is difficult to anticipate when tetracycline or other analogues might return to critically important human usage.

Other classes of antimicrobials (see **Figure 1**) are listed as critically important for both humans and animals. These include the 3rd and 4th generation cephalosporins, quinolones, macrolides, penicillins, and aminoglycosides. These antimicrobial classes point to the value of a One Health approach to surveillance monitoring and conserving existing drugs. However, even among these, the highest priority was assigned to quinolones, 3rd and 4th generation cephalosporins and macrolides. Foodborne pathogens and commensals, like Salmonella, Campylobacter, and *Escherichia coli,* have stirred the greatest concern.

Over time, classes of antimicrobials have shifted from one tier to another.[52] This reflects the dynamic nature of drug resistance patterns. With the challenges in treating Gram-negative infections, polymyxins and monobactams have become reclassified as "critically important." The importance of aminoglycosides in the treatment of endocarditis and the risk of cross-resistance within this family of antimicrobials have prompted placing all of the aminoglycosides into the critically important category. The risk of contracting *Enterococcus* spp. and *Staphylococcus aureus* from food animal sources justifies classifying lincosamides, such as clindamycin, into the highly important category.

In composite, these complementary systems of identifying critically important antimicrobials at WHO and OIE provide a starting point for developing risk assessments from various combinations of pathogens, animal species and drugs. Such an assessment resulted in the FDA's withdrawal of enrofloxacin, a fluoroquinolone antimicrobial, for treating bacterial infections in poultry in 2005. The FDA's Center for Veterinary Medicine established that the use of this fluoroquinolone in poultry was resulting in drug-resistant Campylobacter, a pathogen that transfers to and infects human populations.[53] Enrofloxacin did not eliminate Campylobacter from the intestinal tracts of poultry, but rather selected for bacteria resistant to flouroquinolone drugs. These resistant pathogens ended up on poultry meat in retail outlets. With Campylobacter bacterial infections, serious bouts of such foodborne infections require antimicrobial treatment. Fluoroquinolones would be ineffective in treating such patients if the bacteria exhibit drug resistance, and the prevalence of such drug-resistant infections had risen after enrofloxacin in poultry had been approved for use in the United States.

Such risk assessments underscore the need for surveillance data on drug-resistant bacteria in the food chain, the food commodities in which they are most likely to occur, and to what degree are antimicrobial agents used in food animal production. The withdrawal of specific drugs from use in food animal production also may yield useful data on the costs of switching to alternative approaches. And the processes for establishing critically important antimicrobials for use in human and veterinary medicine may offer useful insights into what drug-pathogen-livestock combinations upon which to focus surveillance and regulatory efforts.

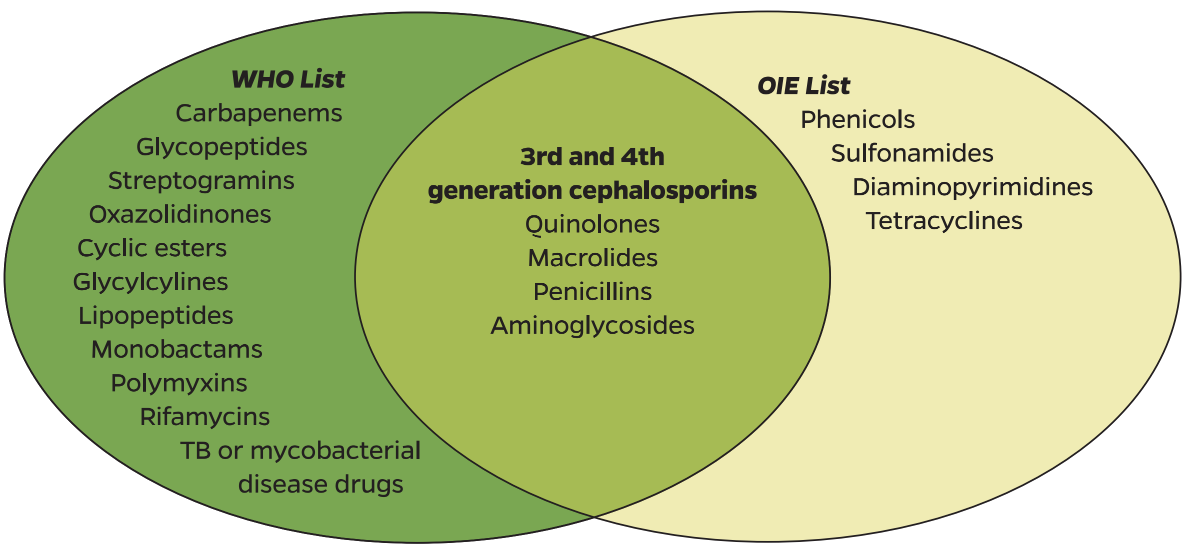
However, co-resistance, or acquisition of mutations conferring resistance to multiple classes of antimicrobials, is an emerging threat to the conservation of critically-important antimicrobials. An example of this phenomenon is the emergence of the methicillin-resistant *Staphylococcus aureus* strain ST398 in Europe in the early 2000s. Co-resistance of the *mec*A gene encoding resistance to beta-lactam antimicrobials and *tet*(M) gene encoding resistance to tetracyclines, combined with uses of tetracyclines in food producing animals, likely played a role in selection for and emergence of this MRSA strain.[54,55] Uses of either beta-lactam antimicrobials (broad-spectrum cephalosporins and penicillins) or tetracycline antimicrobials would be expected to select for this strain. Co-resistance is a source of concern to strategies for intervention that target a single pathogen-drug combination as uses of non-target antimicrobial drugs can select for the target drug-resistant pathogen.

VII.

Structure and Organization of Livestock Production

Intensive production refers to high input-high output systems. These input costs are presumably justified by greater economies of scale and efficiency and notably high livestock densities. By contrast, extensive production involves relatively low inputs. Seventy percent of the 1.4 billion people who comprise the world's extreme poor depend on livestock.[56] No clear pattern exists between what share of livestock production is sold and household income levels. They form part of the extensive system of livestock production. With few livestock per household and even fewer sold, policy attention might be better focused on areas of intensive production.

Figure 1. Critically important antimicrobials for humans and animals



Data Source: WHO, 2012[48] and Codex Alimentarius, 2007[51]

Whether non-therapeutic antimicrobials are used, who makes the decision to apply these drugs, and how these practices are implemented flow from how livestock production is organized. The structure and organization of livestock production also influences how reliant farming operations may be on antimicrobial use. Existing evidence suggests greater use of antimicrobials in intensive production. Large-scale operations are more likely to apply non-therapeutic antimicrobials.[57] For example, 60-70% of larger cattle feedlots in the United States used antimicrobials, often through in-feed additives, whereas only 25-30% of small cattle feed operations did so.[58] Poultry and swine livestock production are particularly well suited for intensification of production because of their high-feed conversion ratios and short generation times.[59] In fact, seventy percent of poultry production and over half of global pork production come from intensive systems.

Switching from the use of antimicrobials in food animal production imposes costs along the value chain. Vertical coordination influences the distribution of risk undertaken by processors and growers. Integrators--where a single firm controls two or more stages in this value chain--can help shift the risk from grower to processor. They can have a variety of contractual arrangements with growers, from providing a market for the food animals to supplying resources for producing the food animals.[60] Reductions in risk can take the form of lowering uncertainty over input costs as well as price and quantity outputs for the farm operation, making production decisions more in line with retailer needs, and ensuring compliance with government regulations. Risk increases with longer growing periods and greater disease susceptibility. Integrators who supply the feed for growers under production contracts would bear the costs of restrictions on antimicrobials. If such restrictions, however, required changes in housing or production practices, such costs might fall on the growers.

Complicating surveillance and monitoring efforts, farm operators may not even know whether the feed received from integrators contain antimicrobials or not. In the United States, such production contracts are common, and as a result, the ARMS cannot fully capture antimicrobial use in their broiler and hog ARMS commodity surveys.[6]

The degree of vertical coordination varies by livestock sector and across different countries. As growers specialize in different lifecycle phases of livestock production, the impact of antimicrobial restrictions may also have disparate impact on these operations. Requirements for veterinary prescriptions for medically important antimicrobials will also be harder to fulfill in areas where independent producers are dispersed over wide geographic areas or where shortages of veterinarians exist. An OIE survey found the infrastructure for veterinary services to be very weak in developing countries, even in countries where animal production contributed significantly to the local economy. Public sector veterinarians were fewer than 35 per million inhabitants in over half the countries, and private sector veterinarians numbered fewer than 100 per million inhabitants. Veterinarians with an animal health mandate numbered fewer than 5.4 per million inhabitants.[61] While training the veterinary workforce is an important goal, perhaps veterinary outreach might be extended with the assistance of telehealth services.

The structure of aquaculture production systems are even more varied as it is practiced with hundreds of species in a variety of water bodies including oceans, estuaries, rivers, ponds, and land-based tanks. Different species of aquatic animals and plants are raised using widely divergent systems and at different scales depending upon local natural resources such as water availability, financial means of the farmer and their production goals, availability of inputs like fish feed, and local cultural norms. Aquaculture can be generally characterized, however, at three different intensities: extensive, semi-intensive, and intensive (Table 1), which combined produce 60 million metric tons per year (excluding aquatic plants) or about half the global supply of seafood.[62]

Table 1. Aquaculture systems, intensification, and antimicrobial use[63]

Culture System	Definition	Antimicrobial use
Extensive	Receive no intentional nutritional inputs but depend on natural food in the culture ecosystem/ facility, including that brought in by water flow e.g., currents and tidal exchange.	Low
Semi-intensive	Depend largely on natural food, which is increased over baseline levels by fertilization and/or use of supplementary feed to complement natural food.	Low
Intensive	Depend on nutritionally complete diets added to the system, either fresh, wild, marine or freshwater fish, or on formulated diets, usually in dry pelleted form.	Low to high, depends on country and species

Extensive aquaculture is the most basic form of aquatic farming where animals are stocked in a water body, and no additional inputs are added into the system. Extensive aquaculture may resemble a hand-dug or natural pond that is stocked with fish such as tilapia or carp and later harvested for family consumption or sale at a local market. Although there are low levels of inputs and outputs, this form of aquaculture is widely practiced throughout the world in resource-limited settings. As access to information, technology, and inputs increases, some farmers are intensifying production and using farm-made feeds or fertilizing ponds with animal waste, which is called semi-intensive aquaculture. In both semi-intensive and extensive aquaculture, there is low use of all inputs, including veterinary medicines, such as antimicrobials.

In intensive aquaculture, farmers stock fish at high densities, provide them a complete feed, and maintain life support systems such as aeration and waste treatment. Intensive aquaculture has grown dramatically since the 1970s and is responsible for the major gains in global fish production. While antimicrobial use is not widely tracked in many aquaculture-producing countries, it is likely that if commercial feed is available, then other inputs, such as veterinary medicines, may also be available.

In both raising livestock and aquaculture, intensive modes of production raise concerns of non-therapeutic use of antimicrobials. Recognizing who controls the inputs of non-therapeutic antimicrobials in vertically integrated livestock or aquaculture production systems though can be key to designing effective policy interventions.

VIII.

Geography of Increased Antimicrobial Consumption

In tackling this global challenge, some regions and countries of the world may contribute disproportionately to the growth in consumption of antimicrobial drugs in food animal production. Between 2010 and 2030, the OECD analysis of these trends shows the importance of China and the United States in this global picture (Table 2).[3] Unchecked, by 2030, antimicrobial consumption tied to rising meat consumption will register significant increases in developing countries, from Indonesia (202 percent) and Nigeria (163 percent) to Vietnam (157 percent) and Peru (160 percent). BRICS countries alone will witness a projected increase of antimicrobial consumption of 99 percent.

Top Five Countries in Global Antimicrobial Consumption in Food Animal Production

2010		2030	
China	23%	China	30%
United States	13%	United States	10%
Brazil	9%	Brazil	8%
India	3%	India	4%
Germany	3%	Mexico	2%

Data Source: Laxminarayan, R et al, 2015[3]

Intensive production also lends itself to geographical concentration. Such production benefits from being proximate to input and output markets as well as to processing and storage facilities. The intensive production of pigs is concentrated in China (64 percent) and high-income areas (24 percent), like the United States and the European Union. China and the United States again lead in the intensive production of poultry, but quite a few other countries also have such operations.[59] The growth in industrial pig and poultry production will give rise to hotspots of increased antimicrobial consumption, particularly in Asia. Of note, aquaculture is growing faster than any other food animal sector.[64]

By analyzing trade patterns, it can be seen that some countries are more reliant on the import and export of livestock and poultry products. With the flow of such trade also comes the risk of transporting drug-resistant pathogens across borders. The U.S. Congressional Research Service studied this problem from a different vantage point: would restricting or prohibiting the use of antimicrobial drugs in animal feed in some countries affect the trade of livestock and poultry products from other countries?[58] In 2009, the United States itself comprised nearly 20 percent of the world's trade in fresh, chilled and frozen beef and pork product exports and 30 percent of the world's trade in fresh, chilled and frozen poultry products. The analysis examined two scenarios, one where global restrictions were not accompanied by U.S. restrictions, and a second where global restrictions were accompanied with U.S. restrictions. For various reasons, however, projecting how these scenarios would unfold is not straightforward. Would the United States lose export markets to countries where food safety concerns over the use of antimicrobials in food products arise? Would other countries with such restrictions in place capture more of the world market of meat production, or are there constraints on the available capacity to produce meat not relying on antimicrobial drugs? Would adopting restrictions in the United States reduce meat production, reduce what might be exported, or increase prices of U.S. meat products?

At the time in 2011, the European Union and New Zealand already restricted the domestic use of antimicrobials for growth promotion in food animals and on similarly imported products treated with such drugs. Since then, further steps towards restricting the use of antimicrobials for growth promotion in the United States have been taken. While short of an effective ban, the FDA has sought voluntary removal of product label indications for growth promotion among animal drug sponsors. However, public health and consumer groups have raised concerns that producers may just relabel their use of antimicrobials as disease prevention rather than growth promotion, thereby not effectively changing their practices. Consumer campaigns have begun to make some gains in encouraging various food outlets to reduce or eliminate antimicrobials in meat products.

IX.

Contextualizing the Costing Framework

Transitioning from the non-therapeutic use of antimicrobials in food animal production may impose costs at various points in the supply chain. Without antimicrobial growth promoters, farmers may have longer wait times till food animals can go to market or may face costs of improving hygienic conditions at their facilities. Vertical integrators similarly may see increased costs as well. But failing to tackle antimicrobial resistance imposes costs on society for near-term gains by food producers—externalities not captured in the cost of food paid by consumers.

Aligning these costs and benefits is a policy challenge, as is common whenever there are externalities. There is some impetus coming from the demand side and from the supply side. On the demand side, consumer groups have called upon retail food outlets curb the use of antimicrobials in the food animal products they source. Responding to such public pressure, five of the top 25 U.S. restaurant chains have announced commitments to curb routine antimicrobial use in meat products they source.[65] On the supply side, the state of the existing literature costing the productivity returns derived from non-therapeutic antimicrobial uses in animal agriculture is limited. In particular, few empirical studies were identified; the large majority involved only modeling. As a result, our confidence in any estimation of the true productivity gain, if it exists, is limited. Moving forward, attempts to quantify productivity gains from non-therapeutic antimicrobial uses must consider other factors that largely influence productivity, including livestock species, geography, and other contextual factors.

However, fully internalizing the externality costs of antimicrobial resistance requires governments to take effective steps to restrict, tax or ban the non-therapeutic use of antimicrobials and engage in the required monitoring and regulatory efforts. In 2006, following bans in multiple countries such as Denmark, Sweden, and Switzerland, the European Union passed regulations to restrict the use of antimicrobial growth promoters across all countries.[66] Similarly, in 2011, South Korea announced a ban on antimicrobial growth promoters in animal feed and committed to developing a system for veterinary oversight of therapeutic use.[67] South Korea also stated that frequent monitoring of feed would occur to check for antimicrobial residues. Besides regulation on non-therapeutic use, Denmark has also imposed a tax on growth promoters beginning in 1998.[68] This tax aims to discourage low-value usage of antimicrobials such as for production purposes.

Applying such a tax across countries, however, requires understanding of the local context. Such a tax may have disparate impacts across differently resourced settings, small and large-scale producers, and livestock sectors. It may also disproportionately impact low- and middle-income countries and small producers for whom it is more difficult to adjust their production processes disproportionately. For example, if producers transition to alternative production methods upon phasing out non-therapeutic use of antimicrobials and if this transition requires significant capital investment, low- and middle-income countries and small farmers may be disadvantaged. Furthermore, the implementation costs may fall differently upon the grower and/or the processor or vertical integrator, depending upon the degree of vertical integration and the nature of the contracts among them.

A society-wide costing framework should consider the benefits and costs of phasing out non-therapeutic use of antimicrobials for all stakeholders. The main beneficiary of reducing the externalities from antimicrobial resistance is society at large – via public health gains. A secondary beneficiary from reducing these externalities are producers who will continue to have access to a broader set of effective antimicrobials for therapeutic use in the future. Traditional research has not considered both of these externality costs in assessing the economic benefits and costs of using antimicrobials in agriculture. Such analysis of externality benefits to consumers and producers should be undertaken in future research.

Since antimicrobial resistance develops over time, the benefits and costs resulting from a ban on non-therapeutic use of antimicrobials depend on the timing of the intervention. The longer it takes to adopt such practices, the more delayed the benefits and the greater the costs. Furthermore, these costs will mount as worldwide meat production continues to rise to meet market demand, and as livestock practices continue to shift to an ever-more intensive production approach.

X.

Proposed Process for Research Agenda

Uses of antimicrobials in industrial food animal production are one aspect of a larger system, in terms of animal health, food quality, and financial returns. Externalities from this system beyond the scope of AMR are not considered here, but are relevant to larger questions of alternative pathways for food production. Potential financial and production benefits of non-therapeutic uses of antimicrobials are enjoyed by industry, and perhaps by extension, through the availability of lower-cost animal protein to consumers. Full evaluation and comparison of these costs and benefits are hampered by critical data gaps.

Prioritizing the research agenda can begin with existing data and projections, but can be refined as data gaps are surmounted. We have described how efforts to conserve critically important antimicrobials, understand the structure and organization of livestock production, and consider the geography of increased antimicrobial consumption might help to focus this undertaking. With stakeholder input, this work needs to be accompanied by assessing the feasibility of collecting such data, both in the near term and over the longer term. To provide credible evidence for policymakers, such research must be conducted independent of financial conflict of interest.

To this end, we recommend the following research agenda designed to address these data gaps. The primary goal of a research agenda focused on economic analysis is to estimate the human disease burden attributable to antimicrobial use in food animals. Collection of antimicrobial use data in food producing animals remains the largest data gap globally. These uses will need to be tied—by geographic location, by animal species or food commodity—to active and passive surveillance systems identifying AMR in isolates from animals, processing plants, food products, and humans.

When considered on a global scale, infrastructure enhancements are needed to drive data collection and surveillance systems. In developing countries, investments in human and physical resources may be required before data collection will be possible. At the international level, infrastructure in the form of harmonized programs and personnel may be needed to coordinate data collection and sharing in a way that will allow analysis of the global food system. Such harmonization should include standardization of laboratory and epidemiologic methodology. Finally, data on the networks of distribution of food animals and commodities are needed. It is critical to recognize that coordination with and compliance from multiple industries is essential to the successful development of a surveillance system that will achieve the intended goal.

The secondary goal of a research agenda is to identify what costs and benefits are associated with antimicrobial drug use in food animal production. Better empirical data are needed on the costs and benefits of antimicrobial uses across different production practices, food animal species, and environments. Such measurements would help parameterize or otherwise inform economic models. Cost analyses and modeling need to move from static to more dynamic modeling approaches that capture the shifts in production practices, consumer demand for meat produced without non-therapeutic use of antimicrobials, and the impact on the trade in food animal products as curbs on non-therapeutic use of antimicrobials are adopted by importing countries. The near- and longer-term impact of curbing non-therapeutic antimicrobial use in food animal production also should be gauged across different settings. The same data on alternative strategies that obviate the need for antimicrobial drug use are critical. Comparison of antimicrobial uses and alternative strategies would allow economic modeling for scenarios under varying conditions of food production in terms of livestock and local context.

A third goal of a research agenda is a broader market analysis for antimicrobial drug use in the industry. Such analysis would involve internal costs and benefits, including pharmaceutical purchase and production gains, and would involve external costs and benefits, including morbidity and mortality burden from human and animal resistant infections attributable to food production uses. In addition, such analysis should consider price fluctuations and potential cost savings that affect consumer demand and access to food animal products. Externalities from antimicrobial uses (in the form of not just human health effects, but ecosystem impacts) should be considered, and have yet to be well measured. Analyses should also capture the externality costs to society due to antimicrobial use in food animal production including the contribution to resistance in human health. Modeling efforts should establish the time-tradeoff for failing to address this problem early and estimate the accrued, additional costs as meat production increases globally and also as practices shift to more intensive livestock production.

A final goal of a research agenda is the ethical evaluation of the distribution of costs and benefits of antimicrobial drug use in food production across stakeholder groups. This would include an analysis of whether the benefits and risks are equitably distributed. To ensure that benefits and risks are equitably distributed, such evaluation could occur on the global scale or within country, considering unique subpopulations that are placed at disproportionate economic or disease risk.

We also recommend consideration of alternative strategies less reliant on these data gaps for implementation and monitoring, including strategies developed within a larger ethical framework that considers issues of sustainability, resilience, local accountability, and food security. A systems thinking perspective would focus on interventions to reduce the demand for meat, to increase the reliance on plant-based proteins, and to shift from industrial food animal production to more sustainable agricultural practices.

Appendices

Appendix I.
Search strategy and selection criteria for review of economic costing analyses of antimicrobials in agriculture

Studies of economic costing of antimicrobials in food animal production were initially identified through a structured search of the literature in PubMed, Web of Science, AgEcon Search, and Google Scholar. The search was narrowed to studies published during 1970-2016 and written in English. Keywords used for the search included combinations of the terms "antibiotic(s)" or "antimicrobial(s)" with either of the terms "economics" or "cost(ing)" also coupled with the terms "livestock", "food animal", "beef", "swine", "pig", "hog", "poultry", "broiler", "layer", "chicken", "fish", "aquaculture", "seafood", "growth promoter", "growth promotion", "subtherapeutic", or "disease prevention". The corresponding Medical Subject Heading (MeSH) terms for these keywords were also searched for within these databases. Among these selected studies, studies from other governmental or intergovernmental agencies were also identified including the World Health Organization, National Academy of Sciences, or Commission on Agricultural Science and Technology.

Articles that did not include costing figures quantifying productivity effects (i.e. average daily growth, feed efficiency, mortality, etc.) in terms of currency were also then excluded. Studies of productivity changes with antimicrobial use, but without costing data, were not included in this review. Converting productivity gains (or losses) into monetary gains (or losses) is context-specific. This briefing note sought to identify available costing figures. Studies were also excluded if they were not published by a peer-reviewed journal, university, governmental agency (i.e. USDA ERS), or intergovernmental organization. Gray literature including commissioned background papers for conferences were also excluded.

Appendix II.
Table of the Literature on the Economic Effect of a Ban on Non-Therapeutic Antimicrobials at the Animal- and Farm-Levels

Author, Study Title, Year	Description of Study	Data Source
Brorsen et al, "Economic Impacts of Banning Subtherapeutic Use of Antibiotics in Swine Production", 2002	Simulation model based on estimates from multiple studies from the 1980s and 1990s of the impact of growth promoters on productivity	Studies from the 1980s and 1990s with data on benefits on feed efficiency, reduced sort loss rate, and reduced mortality rate
Cromwell, "Why and How Antibiotics Are Used in Swine", 2002	Estimates based on previous controlled experiments on impact of growth promoters on productivity	Controlled experimental data on the efficacy of growth promoting antimicrobials on a number of productivity effects including feed efficiency, mortality, and time to market
Miller et al, "Productivity and Economic Impacts of Feed-grade Antibiotic Use in U.S. Pork Production", 2003	Estimates based on observational data over two years from NAHMS were used to estimate productivity effects of antimicrobial growth promoters and then inputted into a swine enterprise budgeting model	Observational study from 1990 and 1995 NAHMS surveys were combined
Liu, Miller, MacNamara, "Do Antibiotics Reduce Production Risk for U.S. Pork Producers?", 2005	Estimates based on observational data from NAHMS were used to estimate productivity effects of antimicrobial growth promoters and then inputted into a swine enterprise budgeting model	Observational study from 2000 NAHMS survey
Miller, Liu, McNamara, and Bush, "Farm Level Impacts of Banning Growth-Promoting Antibiotics in U.S. Pig Grower/Finishing Operations", 2005	Estimates based on observational data from NAHMS were used to estimate the productivity effects of a complete ban and more optimal use of growth promoters before inputting this into a costing model of a farm of 1020 pigs	Observational data from from 2000 NAHMS Survey
Hogberg, Raper, and Oehmke, "Banning Subtherapeutic Antibiotics in U.S. Swine Production: A Simulation of Impacts on Industry Structure", 2009	Using producer cost and performance data and results from Cromwell et al's past research results on the impact of growth promoters on productivity and are then used to simulate the effects of a partial AGP ban and a full AGP ban on representative high, middle, and low-cost producers in different types of swine production operations	Producer cost and performance data from JBS United Feeds, Inc. with physical production data from Cromwell's (2002) comprehensive digest of past research results comparing AGP and AGP-free production throughout the swine production stages
WHO, "Impacts of antimicrobial growth promoter termination in Denmark", 2002	Observational data based on producer records were collected looking at before and after effects of the ban on antimicrobial growth promoters on productivity measures in Denmark	Data from Finn K. Udesen from the National Committee for Pigs Data on broiler productivity collected by the Danish Poultry Council

[*]All costing figures have been adjusted to 2015 $USD using the Bureau of Labor Statistics Inflation Calculator: http://www.bls.gov/data/inflation_calculator.htm

Livestock Sector	Indication of Antimicrobial Use	Effect quantified	Cost of Using Non-therapeutic Antimicrobials*
Swine	Growth Promotion	Decreased feed efficiency, mortality, and sort loss	$3.66 per animal
Swine	Growth Promotion	Decreased feed efficiency and mortality and increased number of days to market and feed input	$2.99 per animal
Swine	Growth Promotion	Loss in profits based on growth promoter increases on average daily gain, feed efficiency, and the mortality rate in grower/finisher operations	$0.76 per animal
Swine	Growth Promotion	Loss in profit due to changes in variation of pig live weight	$1699 per farm
Swine	Growth Promotion	Loss in profit due to changes in variation of average daily gain, feed conversion ratio, mortality rate, and stunted rate	$1748 for 1020-head barn
Swine	Growth Promotion	Loss in profit due to decreased litter per sow, survival rate of piglets, average daily gain, and variation in number of attendant changes as well as increased labor costs	High-cost farm: $6.39 (farrow to finish), -$3.30 (breed to wean), $9.71 (wean to finish); Medium-cost farm: $4.89 (farrow to finish); -$2.07 (breed to wean), $10.98 (wean to finish); Low-cost farm: -$1.49 (farrow to finish), -$3.42 (breed to wean), $3.92 (wean to finish)
Swine	Growth Promotion	Increased excess mortality, number of feeding days to achieve target live weight, use of therapeutic antimicrobials, and labor	$1.45 per animal
Poultry			$0 per animal

Appendix II.
Table of the Literature on the Economic Effect of a Ban on Non-Therapeutic Antimicrobials at the Animal- and Farm-Levels

Author, Study Title, Year	Description of Study	Data Source
Graham, Boland, Silbergeld, "Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis", 2007	Experimental data results from industry-run study on productivity effects of growth promoters were inputting into an economic model developed by the authors using cost and payment data from the literature	Data from Perdue Farms, Inc. of a three-year non-randomized controlled trial of poultry grown without AGPs
MacDonald and Wang, "Foregoing Sub-Therapeutic Antibiotics: The Impact on Broiler Grow-out Operations", 2011	Observational data from ARMS survey was compared between producers that used subtherapeutic antibitoics versus those that do not in terms of productivity measures and contract fees	Data from 2009 ARMS Survey
Mathews, "Economic Effects of a Ban Against Antimicrobial Drugs Used in U.S. Beef Production", 2002	Costing minimization and partial equilibrium model estimating the economic impact of 3 different scenarios of antimicrobial drug use in beef cattle production including a no-ban scenario and two levels of bans (full and partial ban) for an individual producer	Data from the National Research Council's "Nutrition Requirements of Beef Cattle" and pricing data from USDA
Lawrence and Ibarburu, "Economic analysis of pharmaceutical technologies in modern beef production", 2007	Estimates through a Monte Carlo simulation of the costs of eliminating subtherapeutic antimicrobials use across beef cattle production segments	Data from more than 170 research trials evaluating pharmaceutical technologies in the cow-calf, stocker, and feedlot segments of beef production and pricing data developed based on prices reported by the USDA Agricultural Marketing Service

All costing figures have been adjusted to 2015 $USD using the Bureau of Labor Statistics Inflation Calculator: http://www.bls.gov/data/inflation_calculator.htm

Livestock Sector	Indication of Antimicrobial Use	Effect quantified	Cost of Using Non-therapeutic Antimicrobials*
Poultry	Growth Promotion	Increased mortality rates, decreased average weight gain, decreased feed efficiency	$0.0093 per animal
Poultry	Growth Promotion and Disease Prevention (characterized as “Subtherapeutic Use)	Changes in feed-conversion ratio, contract fees to integrators	Found no statistically significant difference in production measures but found higher contract fees (2.1% greater) for farms using antimicrobials only for therapeutic purposes
Beef Cattle	Growth Promotion and Disease Prevention (described as low, subetherapeutic levels of antimicrobial drugs - LLADs)	Increased average cost per pound of gain as well as change in cost of feed and yardage	Increase of $0.06 (Full Ban) and $0.0342 (Partial Ban); Increase of $6.25 per head (Full Ban) and $12.46 (Partial Ban)
Beef Cattle	Subtherapeutic antibiotics (unspecified)	Increased production costs per animal	Increase of $11.06 (stocker operations) and $6.77 (beef feedlots)
		Percentage increase in cost of production	Increase of 0.56 percent

Appendix III.
Table of Literature on Economic Effect of a Ban on Non-Therapeutic Antimicrobials at the Market Level

Author, Study Title, Year	Description of Study	Data Source
Allen and Burbee, "Economic consequences of the restricted use of antibiotics at subtherapeutic levels in broiler and turkey production", 1972	Estimates of the effects on market price and quantity of a ban on subtherapeutic antibiotic across varied producer scenarios across output and length of feeding time, assuming no suppy response	Data on productivity due to antimicrobials obtained from FDA reports and other sources of experimental data; data on costing from USDA
Gilliam and Martin, "Economic importance of antibiotics in feeds to producers and consumers of pork, beef and veal", 1975	Estimates of economic effects of a ban on antibiotic feed additives under livestock output, price, and cost conditions under 2 scenarios where producers continue to feed larger numbers of livestock for the same period of time to maintain output levels or where producers continue to feed the same number of livestock for same period of time as before the ban, assuming no supply response	Experimental data from the 1960s
Dworkin, "Some economic consequences of restricting the subtherapeutic use of tetracycline in feedlot cattle and swine", 1976	Estimates modeling the changes in quantity and price due to ban on tetracycline with and without substitutes, assuming no supply response	Expermental productivity from the 1960s
Mann and Paulsen, "Economic impact of restricting feed additives in livestock and poultry production", 1976	Quarterly simulation model of meat market between 1973-1977 under 2 scenarios where no substitutes were available and viable substitutes would be available after 1 year	Empirical productivity data from 1962 to 1972

All costing figures have been adjusted to 2015 $USD using the Bureau of Labor Statistics Inflation Calculator: http://www.bls.gov/data/inflation_calculator.htm

Livestock Sector	Indication of Antimicrobial Use	Effect quantified	Cost of Using Non-Therapeutic Antimicrobials*
Poultry	Growth Promotion	Changes in quantity produced	Decrease of 2.244 percent (chickens) and 3.184 percent (turkey)
		Changes in market price	Increase of 22.48 percent (chickens) and 13.710 percent (turkeys)
		Changes in production costs (broilers)	Increase of $33.58 to $23.4 million (depending on assumptions)
		Changes in retail price per pound (broilers)	Increase of $0.17 to $12.92 (depending on assumptions)
Beef Cattle, Swine	Growth Promotion	Change in total industry-wide production costs	Increase of $1.42 billion (beef) and $2.85 billion (swine)
		Change in total retail price per pound	Increase of $0.0.89 (beef) and $0.31 (swine)
Beef Cattle, Swine	Subtherapeutic Use	Change in quantity	Decrease of 1.01 percent without substitutes and 0.57 percent with substitutes (beef); Decrease of 4.09 percent without substitutes and 0 percent wth substitues (swine)
		Change in price	Increase of 4.8 percent without substitutes and 1.18 percent with subtitutes (beef); Increase of 11.21 percent without substitutes and 0.60 percent with substitutes (swine)
Beef Cattle, Swine (Pigs/ Hogs), Broilers, Turkey	Subtherapeutic Use (unspecified indication)	Change in costs per animal	Increase of $19.58 (beef), $3.04 (pig), and $36.03 (hog)
		Change in quantity	Decrease of 0.101 (beef) and 0.0409 (pig) percent
		Change in market price	Increase of 0.048 (beef) and 0.1121 (pig) percent

Appendix III.
Table of Literature on Economic Effect of a Ban on Non-Therapeutic Antimicrobials at the Market Level

Author, Study Title, Year	Description of Study	Data Source
USDA, "Economic effects of a prohibition on the use of selected animal drugs", 1978	Econometric simulation model across all livestock sectors estimating market outcomes 1 and 5 years after a ban on subtherapeutic antimicrobials	Experimental productivity data from 1950s and 1960s
Wade and Barkley, "The economic impacts of a ban on subtherapeutic antibiotics in swine production", 1992	Econometric supply and demand model estimating the impact of ban on subtherapeutic antimicrobials on the price and quantity of pork	Quarterly data from 1959 to 1989 from the USDA
National Research Council, "The Use of Drugs in Food Animals: Benefits and Risks", 1999	Econometric analysis of production costs of a ban on subtherapeutic antimicrobials holding price and quantity constant	Data from expert panel
Mathews, "Antimicrobial drug use and veterinary costs in U.S. livestock production." 2002	Econometric supply and demand model estimating the impact of low-level antimicrobial use on swine production and price	2000 price and cost data reported to USDA
Mathews, "Economic Effects of a Ban Against Antimicrobial Drugs Used in U.S. Beef Production", 2002	Costing minimization and partial equilibrium model estimating the economic impact of 3 different scenarios of antimicrobial drug use in beef cattle production including a no-ban scenario and two levels of bans (full and partial ban) for an individual producer	Data from the National Research Council's "Nutrition Requirements of Beef Cattle" and pricing data from USDA
Hayes, Jensen, Fabiosa, et al. Economic Impact of a Ban on the Use of Over-the-Counter Antibiotics, (1999)"Economic Impact of a Ban on the Use of Over the Counter Antibiotics in U.S. Swine Rations." (2001), "Technology choice and the economic effects of a ban on the use of antimicrbial feed additives in swine rotations"(2002)	Quarterly eonometric simulation modeling productivity effect data after Swedish ban to the the U.S. market over a 10-year period	Information gathered during a visit to Sweden and Denmark, and from other sources and input cost data reported to the USDA
Hayes,, Jensen, "Lessons from the Danish Ban on Feed-grade Antibiotics", 2003	Eonometric simulation modeling productivity effect data after Danish ban to the the U.S. market over time	Information gathered during a visit to Sweden and Denmark, and from other sources and input cost data reported to the USDA
USDA/ERS, "Economics of Antibiotic Use in U.S. Livestock Production", 2015	Econometric supply and demand model of a ban on antimicrobial use for production-purposes across livestock sectors and its impact on market price and quantity	ARMS and NAHMS data reported to the USDA

All costing figures have been adjusted to 2015 $USD using the Bureau of Labor Statistics Inflation Calculator: http://www.bls.gov/data/inflation_calculator.htm

Livestock Sector	Indication of Antimicrobial Use	Effect quantified	Cost of Using Non-Therapeutic Antimicrobials*
Beef Cattle, Swine, Broilers, Turkey	Subtherapeutic Use (unspecified indication)	Changes in price (Year 1)	Increase of 15.02 (hogs), 12.99 (broilers), and 1.68 (beef) percent
		Changes in price (Year 5)	Increase of 1.14 (hogs), 2.25 (broilers), and 0 (beef) percent
		Changes in quantity (Year 1)	Decrease of 4.86 (hogs), 8.24 (broilers), and 0.19 (beef) percent
		Changes in quantity (Year 5)	Decrease of 0.84 (hogs), 2.16 (broilers), and increase of 0.30 (beef) percent
Swine	Growth Promotion and Disease Prevention (described as Subtherapeutic Use)	Change in price	Increase of 3.2 percent
		Change in quantity	Decrease of 2.8 percent
Beef Cattle, Swine, Chicken	Growth Promotion and Disease Prevention	Change in price per pound	Increase of $0.02 - $0.04 (chicken) and $0.04 - $0.08 (beef, pork)
Swine	Low-level Use (unspecified indication)	Change in price	Increase of $1.03
Beef Cattle	Growth Promotion and Disease Prevention (described as low, subetherapeutic levels of antimicrobial drugs - LLADs)	Changes in production costs	Decrease of 9 percent
		Changes in price	Increase of 3 percent
Swine	Growth Promotion and Disease Prevention (described as Antimicrobial Feed Additives)	Change in productions cost per animal	Increase of $8.61 in Year 1 and decline over 10 years
		Change in profits per animal	Decrease of $5.93 in Year 1 and decline over 10 years
Swine	Growth Promotion	Changes in production cost per animal	Increase of $5.80
		Change in retail price	Increase of 2 percent
Beef Cattle, Dairy Cattle, Broilers, Swine	Growth Promotion	Changes in wholesale price	Increase of 1 percent
		Changes in output	Decrease of 1 to 2 percent

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