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ANNUAL REVIEWS

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External Societal Costs of Antimicrobial Resistance in Humans Attributable to Antimicrobial Use in Livestock

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antimicrobial resistance, AMR, animal agriculture, human health, societal cost, externality

Abstract

Antimicrobial use (AMU) in animal agriculture contributes to antimicrobial resistance (AMR) in humans, which imposes significant health and economic costs on society. Economists call these costs negative externalities, societal costs that are not properly reflected in market prices. We review the relevant literature and develop a model to quantify the external costs of AMU in animal agriculture on AMR in humans. Parameters required for this estimate include (*a*) the health and economic burden of AMR in humans,

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(*b*) the impact of AMU in animal agriculture on AMR in animals, (*c*) the fraction of AMR in humans attributable to animal agriculture, and (*d*) AMU in animals. We use a well-documented historic case to estimate an externality cost of about US$1,500 per kilogram of fluoroquinolones administered in US broiler chicken production. Enhanced data collection, particularly on the third and fourth parameters, is urgently needed to quantify more fully the externalities of AMU in animal agriculture.

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INTRODUCTION

The rising rates of antimicrobial resistance (AMR) in bacterial populations threaten treatment options for these infections globally (35). The selective pressures created by antimicrobial use (AMU) and misuse in both humans and animals have led to widespread AMR in a broad range of commensal and pathogenic bacteria (62). Similar to AMU in humans, AMU in animal agriculture can promote AMR in animal and human pathogen populations, which imposes significant health and economic costs on society (44, 47, 62). Moreover, these costs are what economists call externalities, meaning the costs are side effects of AMU that affect society and that are not properly reflected in the price of antimicrobials, creating a case for public policy intervention.

The focus of this review is to assemble and evaluate the literature on the entire pathway through which AMU in animal agriculture contributes to AMR in the human population. We propose a model to estimate the external societal costs of AMU in animal agriculture. The parameters required to inform this estimate include (*a*) the health and economic burden of AMR in humans, (*b*) the impact of AMU in animal agriculture on AMR, (*c*) the fraction of AMR in humans attributable to animal agriculture, and (*d*) AMU in animals (**Figure 1**). We then present a historic case study—the application of the fluoroquinolone antibiotic enrofloxacin to US broiler chickens—and quantify the societal externality costs generated in the form of the additional fluoroquinolone resistance (FR) of one specific pathogen, *Campylobacter* spp., in the United States in 1999, before the use of fluoroquinolones was banned in the chicken industry. We find an externality cost of US$1,500 per kilogram of enrofloxacin applied. More generally, the estimates produced by our model could provide guidance for policy interventions to address the growing public health crisis of AMR.

TOTAL HEALTH AND ECONOMIC BURDEN OF AMR IN HUMANS

AMR significantly increases the morbidity, mortality, hospital length of stay (LOS), direct health care–related costs, and indirect societal costs of infections (33, 65). This section reviews the literature on the health and economic impact of AMR in humans. An overview of the studies and reports included in this review are provided in the **Supplemental Material** (**Supplemental Table 1**, **Supplemental Discussions 1** and **2**).

Supplemental Material >

Health Impact of AMR

The UK Review on AMR, using studies commissioned by RAND Europe and KPMG, sought to quantify the future worldwide health and economic impacts of AMR (28, 48). The UK Review on AMR estimated that 700,000 deaths per year are currently attributable to AMR, including from malaria, HIV, and tuberculosis (34). For *Enterobacteriaceae*, for example, Temkin et al. (49) estimated a total of 6.4 million bloodstream infections (BSIs) and 50.1 million "serious infections" caused by third-generation cephalosporin-resistant (3GCR) and carbapenem-resistant

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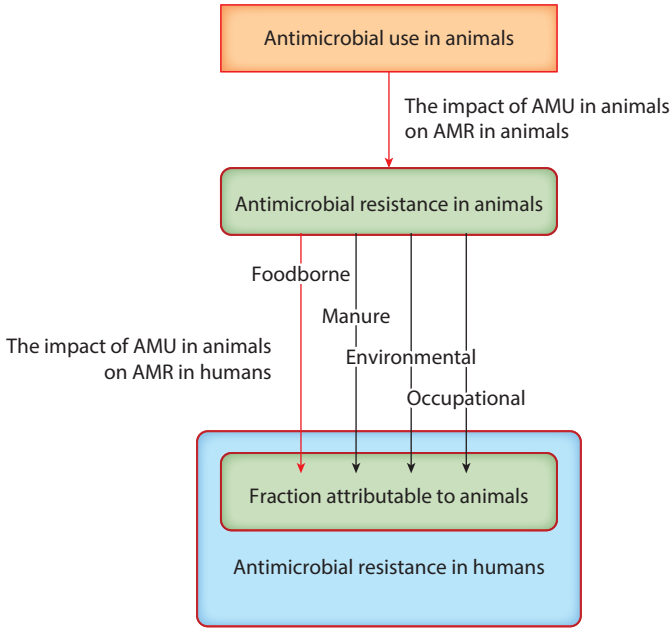

Figure 1

Framework for externality cost of antimicrobial resistance (AMR) from antimicrobial use (AMU) in animal agriculture. This diagram illustrates the parameters that could enter the modeling of this externality. The red lines represent parameters with sufficient data for inclusion and comprise a conservative estimate of this parameter. The black lines represent parameters where insufficient data existed to inform the estimation of this externality at this time, but which would have increased the externality cost. Parameter compartments were not drawn to scale.

(CarR) *Escherichia coli* and *Klebsiella pneumoniae* worldwide in 2014. However, all available global estimates were hindered by poor surveillance and reporting in Asian and African countries (31, 34, 49). A World Health Organization (WHO) report also documented that AMR surveillance is neither coordinated nor harmonized, and many gaps exist on bacteria of major public health importance (60). Global estimates thus require that AMR infection rates for many countries are imputed using established AMR surveillance systems, such as the European Antimicrobial Resistance Surveillance Network (EARS-net) data (34, 49).

Higher-quality data allow for more reliable national-level estimates for the United States and the European Union/European Economic Area (EU/EEA). For the United States, Thorpe et al. (50), using US Agency for Healthcare Research and Quality (AHRQ) Medical Expenditure Panel Survey (MEPS) data, estimated an average of 1.2 million AMR infections each year from 2002 to 2014. During this timeframe, the number of infections remained approximately constant; however, the proportion of infections due to antimicrobial-resistant pathogens has more than doubled, from 700,000 to 1.6 million AMR infections (50). Thorpe et al. did not comment on the attributable mortality due to AMR infections; however, the US Centers for Disease Control and Prevention (CDC) has estimated more than 2,868,700 AMR infections and 35,900 deaths annually using 2017 data (5a). An alternative estimate carried out by Washington University in St. Louis investigators places the number of deaths at more than 4 times the CDC estimate (3). For EU/EEA countries, Cassini et al. (4), using EARS-net data, estimated a total of 671,689 cases of AMR infection in 2015, resulting in 33,110 deaths and 874,541 DALYs (disability-adjusted life years) from 5 types

of infections with 8 different antimicrobial-resistant bacteria. Among EU/EEA countries, Italy and Greece had the highest mortality rates from AMR, with about one-third of AMR-attributable deaths in all EU/EEA countries occurring in Italy. The study also found that a substantial burden of AMR infections in the EU/EEA were attributable to community-associated infections (almost 40%) (4).

In low- and middle-income countries (LMICs), AMR rates are currently high and projected to grow more rapidly than in developed countries (36). In the Russian Federation, India, and Brazil, 40–60% of recorded bacterial infections are due to antimicrobial-resistant pathogens, compared with an average of 17% in Organisation for Economic Co-Operation and Development (OECD) countries (36). Data and results provided by the WHO Global Antimicrobial Resistance Surveillance System (WHO GLASS) will be valuable in providing accurate and standardized data to inform estimates on the current and projected health impacts of AMR, especially for LMICs (61).

Economic Impact of AMR

Estimates on the economic impact of AMR have adopted two complementary perspectives. A majority of studies have utilized a health care/payer perspective: to report excess health care–related expenditures associated with the treatment of AMR (33, 65). Several recent reports have incorporated a societal perspective to report the loss of economic output due to AMR (33, 64, 65). A summary of the future economic impacts of AMR, based on multiple different projected trends of AMR and infection rates to 2050, is provided in the **Supplemental Material**. The section below focuses on current estimates on the incremental treatment cost of AMR and the total economic impact of AMR for the United States, including direct health care–related costs and indirect societal costs.

Supplemental Material >

The current variability in available estimates on the incremental treatment costs of AMR is attributed largely to inconsistencies in adjusting for critical covariates, such as hospital LOS prior to onset of infection, disease severity, and inappropriate antibiotic use (8, 20, 65). Using a risk bias assessment tool, Wozniak et al. determined that the best estimates for antimicrobial-resistant bacteria–specific incremental treatment costs are currently available for methicillin-resistant *Staphylococcus aureus* (MRSA), 3GCR-*Enterobacteriaceae*, and extended spectrum beta lactamase-producing (ESBL)+*Enterobacteriaceae*, ranging from 1,600 EUR per MRSA BSI (nonsignificant) to 9,473 Swiss Francs (CHF) per ESBL+*Enterobacteriaceae* BSI (45, 46, 65). Excess LOS ranged from an additional 2.54 days per MRSA BSI (nonsignificant) to 6.8 days per ESBL+*Enterobacteriaceae* (significant) (45, 46).

For the United States, Thorpe et al. found that AMR added an average of US$1,383 in incremental costs to bacterial infection treatment and estimated an average annual national health care expenditure of US$2.2 billion due to AMR (50). Most of these cost estimates were associated with increased costs from inpatient care, which reflects both additional LOS and additional cost of prescription drugs. This figure aligns with the US model produced by the OECD (36). The CDC reported a higher excess expenditure of US$20 billion in annual health care costs and US$35 billion in societal costs due to AMR (5). The increased figures produced by the CDC may be due, in part, to the use of cost data from a single urban hospital in the United States, which did not compare AMR infections to susceptible infections (43).

Taken together, most papers aimed at understanding the health and economic impacts of AMR have consistently concluded that AMR is a major public health issue that will grow significantly if no effective national- and global-level actions are implemented. Despite heterogeneity in estimates, the current and projected impacts of AMR demand urgent countermeasures. One such measure, advocated by the WHO, the World Organisation for Animal Health (OIE), and the

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Food and Agriculture Organization (FAO), is the reduction and prospective restriction of AMU in animal agriculture (18, 37, 62).

THE IMPACT OF AMU IN ANIMAL AGRICULTURE ON AMR

AMU in food animals is one of several factors that promote AMR in both animals and humans (34, 44, 47). Many antimicrobials administered to food animals are the same classes as those utilized in medicine for humans. Genetic determinants that confer AMR can be transmitted among both commensal and pathogenic bacteria, including all zoonoses (19). Pathways that transmit bacteria (and antimicrobial-resistant bacteria) between humans and animals include direct contact, such as occupational exposure to animals, and indirect contact, such as foodborne and environmental routes of transmission (63). The use of colistin in animal agriculture in China provides a recent example of the emergence, selection, and widespread dissemination of genetic determinants of AMR as a probable consequence of AMU in animal agriculture (59). Administration of colistin in food animals is believed to have selected for a novel resistance gene, *mcr-1*, in chicken and pig *E. coli* isolates in China, which has subsequently been reported in more than 30 countries (30, 57). Consequently, China has banned the use of colistin administration in feed additives (57).

In recent years, many countries, including the United States, Canada, Japan, and China, have limited, or restricted, the use of antibiotics in food animals (14, 23, 51, 57). In some cases, such restrictions have been associated with reductions in AMR in humans, suggesting a causal relationship between AMU in animals and AMR in humans (47). In this section, we first summarize the reasons for AMU in animals. Second, using the results of two independent reviews, commissioned by the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), and the culminating WHO AGISAR report, we focus on the impact that restricting AMU in animals has on AMR in animals and humans.

AMU in Animals

Antimicrobial drugs are used in four different ways in food animals: treatment, metaphylaxis, prophylaxis, and growth promotion (53). Treatment uses are intended for animals with definitive signs or diagnostic tests that suggest a bacterial infection. Used interchangeably with disease control, metaphylaxis is the process of administering antimicrobials to animals without clinical symptoms of infection that have been exposed to infected animals in the same population. A more liberal use of antimicrobials is prophylactic use, also known as disease prevention. Prophylaxis is used to prevent animal disease among populations at risk of infection, although no animals display clinical illness and no infectious agent exposure is confirmed. Although prophylaxis and metaphylaxis antimicrobial regimens do not explicitly treat animals with clinical illness, these practices are widely believed to prevent disease and reduce economic costs for producers (21). Lastly, growth promotion is the practice of administering antimicrobials to animals because they increase animal growth rates.

Using medically important antimicrobials (MIA) for growth promotion is regarded by the WHO, the FAO, and the OIE as an inappropriate AMU (18, 37, 62). These international agencies, among others, state that treatment is necessary for animal welfare and health; however, stakeholders have various levels of tolerance to include metaphylactic, prophylactic, and growth promotion uses in the definition of treatment. For example, the WHO's recommendation of a "complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed" has not resulted in similar commitments by the FAO and the OIE. Furthermore, some stakeholders are concerned

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that AMU labeled for prophylaxis or metaphylaxis may be used instead by some groups for growth promotion.

The Impact of AMU in Animal Agriculture on AMR in Animals

Limiting AMU in food animals was associated with decreased prevalence of antimicrobial-resistant bacteria in many studies (44). A meta-analysis by Tang et al. (47) described 179 studies aimed at assessing this effect. One such study in Japan showed that following a voluntary withdrawal of a third-generation cephalosporins in 2012, the prevalence of broad-spectrum cephalosporin-resistant *E. coli* (BSCR-*E. coli*) isolates from healthy broilers decreased from 16.4% in 2010 to 4.6% in 2013 (23). Using 81 of these studies, Tang et al. reported negative risk differences ranging from −1% for cephalosporin-resistant *Enterobacteriaceae* in fecal samples to −39% for macrolide-resistant *Enterococcus* spp. in fecal samples, corresponding to a 1–39% reduction in the proportion of antimicrobial-resistant isolates among animals with restricted AMU compared to isolates with AMU (47). The greatest risk difference was observed for *Enterococcus* spp. and the least for *Campylobacter* spp. The risk differences, although significant regardless of animal type, appeared greater in magnitude for interventions that targeted pigs and poultry, which are typically raised in intensive conditions where interventions occur at the herd or flock level (47). The World Bank report noted that AMR in animals would, over time, likely result in lower livestock production owing to greater prevalence of untreatable disease—a burden expected to be more pronounced in LMICs (64).

The Impact of AMU in Animal Agriculture on AMR in Humans

Studies that directly aimed to address the association between restricted AMU in animals and reduced antimicrobial-resistant bacteria in humans are more scarce but have supported a similar conclusion: AMU restriction in animals was associated with decreases in antimicrobial-resistant bacteria in humans (34, 44, 47). Tang et al. found only 21 studies that assessed the impact of AMU restriction in food animals on AMR in humans. Scott et al. determined that only one study provided this evidence with credible effect sizes and time sequences (44, 62). This single study showed that the voluntary discontinuation of ceftiofur use in chicken hatcheries in Canada in 2005, and partial reintroduction in 2007, was associated with respective decreases and increases in ceftiofur-resistant *Salmonella* Heidelberg in samples from both chicken meat and humans (14). This temporal trend suggests a potential causal link between AMU in animal agriculture and AMR in humans. Tang et al. (47), using data from 13 of these studies, concluded that the prevalence of antimicrobial-resistant bacteria in human samples was 24% lower in the intervention group, where the use of antibiotics in animals was reduced compared with the control group. Owing to the limited number of studies assessed, Tang et al. did not produce isolate-level pooled risk differences stratified by bacterial species or sample type. The pooled risk difference was stronger in farm workers compared with humans without direct contact with livestock animals (47). This finding is consistent with ongoing work in North Carolina, United States, that demonstrates an increased risk of *S. aureus*, including multidrug-resistant *S. aureus* and MRSA, carriage and infections among industrial hog operation workers (22, 58).

Despite the limited evidence linking AMU in animals to AMR in humans, the WHO AGISAR strongly recommends "an overall reduction in the use of all classes of MIA in food-producing animals," including a complete restriction on the use of MIA for growth promotion and disease prevention purposes (62). It is important to note that determining causality between AMU in animals and AMR in humans requires studies designed around restrictions of AMU in animals

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and thus must be conducted within critical windows of opportunity that are temporally aligned with state- or national-level regulatory or statutory action. For example, Senate Bill 27 in California, United States, effective in 2018, banned AMU for the purpose of growth promotion and prohibited the use of MIA in livestock unless ordered by a veterinarian (S.B. 27, Chapter 758).

THE FRACTION OF AMR IN HUMANS ATTRIBUTABLE TO ANIMAL AGRICULTURE

AMR can spread to humans through direct and indirect pathways. In animal agriculture, direct pathways (i.e., animal contact) largely affect agricultural workers (63). Conversely, indirect pathways largely involve consumer populations. Indirect exposures include animal food products and animal waste through the contamination of groundwater (63). The exact extent to which AMR in animals contributes to AMR infections in humans has not been established, complicated primarily by the bidirectional flow of genetic determinants of drug resistance that exists between animal and human pathogen populations. Although the CDC has estimated that one in five AMR bacterial infections are linked to food or animals, an accurate fraction of AMR human infections attributable to livestock via all pathways may currently be infeasible (5). Therefore, we focus our model parameterization on the human infections attributable to animal agriculture via a foodborne pathway.

Several countries have promulgated surveillance systems to monitor indirect, foodborne illness–related infections, which in recent years have provided estimates on animal source attribution. Owing to limitations in current and active surveillance for direct mechanisms, we can review only the proportion of human infections attributable to animals from foodborne illnesses.

An expert panel from the WHO was tasked with this question of AMR source attribution. We list results for three bacteria: *Campylobacter*, *Salmonella*, and *E. coli*. For complete, in-depth regional analysis, we refer readers to the resulting publication (24). Without exception, the primary source of human campylobacteriosis was poultry meat, accounting for 40% in European regions to more than 50% in American, African, and Eastern Mediterranean regions. Foodborne salmonellosis was caused by poultry products in more than 30% of cases in the African and Eastern Mediterranean regions. Among European regions and in a subregion of the Western Pacific and Southeast Asian region, pork accounted for 15–20% of salmonellosis cases. Aside from the Southeast Asian region, *E. coli* foodborne illness was attributed primarily to beef, with more than 25% of *E. coli* infections sourced from beef products (24).

The US Department of Agriculture, the US Food and Drug Administration (FDA), and the CDC comprise the Interagency Food Safety Analytics Collaboration (IFSAC), a surveillance system that surveys foodborne illness via outbreak data in the United States. Using data from 1998 through 2016 in the United States, the IFSAC reported that 9 million people fall ill, 56,000 are hospitalized, and 1,300 die of foodborne diseases annually (25). More than 75% of 2016 Salmonellosis illnesses were from 7 food categories, and the second-largest source (behind seeded vegetables) was chicken (12.7%) (25). In 2016, more than 70% of *E. coli* O157 outbreaks were sourced from vegetable crops and beef, and more than 70% of *Listeria monocytogenes* cases were from the consumption of dairy and fruit. In 2016, chicken was the primary source for nondairy-related campylobacteriosis cases at 47.5% (25). Contemporaneously, the National Food Institute attributed 46% of *C. jejuni* cases in Denmark to domestic chicken, 19% to cattle, and 9% to imported chicken (40). Because multiple factors are associated with the attributable fraction, estimates likely vary among countries (24).

Regional- and national-level surveillance systems for foodborne pathogens estimate the proportion and total number of infections attributable to animal agriculture. Such surveillance

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systems are currently exemplified best by the North American and EU/EEA systems. However, surveillance systems should be expanded to comprehensively monitor antimicrobial-resistant bacteria attributable to animal agriculture contracted via direct routes of exposure (e.g., occupation workers) and other, nonfoodborne environmental routes of exposure (e.g., contaminated waterways) (15).

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AMU IN ANIMALS

Properly estimating the effects of AMU in animal agriculture requires data on the use of antimicrobials. The ideal data set would report the exact dose of active antimicrobial ingredient administered, the number of animals that received it, and the exact reasons for administration. Unfortunately, AMU data in animal agriculture are largely unavailable in most countries. Cuong et al. (10) provide one of the only reviews of AMU in animal agriculture across all countries worldwide. Many of the reviewed manuscripts do not elucidate exact AMU amounts and therefore cannot be incorporated into our proposed economic model. Inclusion would also require the data to be stitched together across studies, which, even collectively, may not accurately represent the target population. This section focuses on antimicrobial sales (AMS) to the domestic animal agriculture sector as a substitute, on which significantly more data are available. **Supplemental Discussions 3** and **4** describe methodologies for data acquisition and the trends and projections described in the reviewed material. The total kilograms (kg) of antibiotics bought by the animal agriculture sector within a country will necessarily be less than or equal to what is used in the sector.

Supplemental Material >

More antimicrobial agents are sold in the United States for domestic animal production, both MIA and nonmedically important (NMIA), than in any other country (10.9 million kg) except perhaps for China, about 40% more than the entirety of the European Union (7.79 million kg), according to compiled country- and region-reported data (13, 17). About 50% of AMS in the United States were NMIA (5.4 million kg), whereas the European Union sold no NMIA for use in animal agriculture (13, 17). Thus, with regard to MIA, the European Union sold 30% more antimicrobials to the animal agriculture sector than did the United States (**Supplemental Table 2**).

All other countries reported official AMS data at fractions of those found in the United States and the European Union. However, estimates for China have ranged from 6 million kg in 2001 to 84.2 million kg in 2013, with upper limits around 8 times more than the United States and 11 times more than the European Union (16, 66). These figures for China are highly disparate from the OIE estimates of the entire Asian continent, estimated to be ~3 million kg (38).

Comparison of sales of individual classes of antimicrobial drugs by weight demonstrates that tetracyclines constitute the largest portion of AMS and make up 51% of all antimicrobials by weight sold in Canada, 47% in Japan, 33% in Korea, 32% in the United States, 29% in the European Union, and 9% in Australia (1, 7, 13, 17, 32, 42). Tetracyclines are sold four times more than any other antimicrobial class in countries that reported sales to animal agriculture (**Supplemental Table 2**). The antimicrobial class with the lowest number of sales is cephalosporins, which contribute 0.3% of total sales among countries surveyed and under 1% of the composition of each individual country's AMS. However, comparisons by weight do not take the relative potencies of the drugs into account; some antimicrobials require either lower concentrations or a smaller dose (by weight) than do others to achieve the same health or production end points.

Given different dosing requirements for different species of animals, estimates of AMS or AMU should ideally be stratified by animal species and standardized to the total number of that animal species raised for meat. This standardization would allow direct comparisons of antimicrobials sold (and used) per animal produced in each sector of animal agriculture among

different countries and may give insight into use, animal husbandry, and animal welfare practices. A Natural Resources Defense Council (NRDC) report estimated that in 2017, the United States used 155.5 mg of antibiotics per kg of livestock (mgA/kgL), whereas some EU countries used 40.8 mgA/kgL (Denmark) and 45.0 mgA/kgL (United Kingdom) (26). However, other countries such as Italy and Spain consume about 2 times more per kg of livestock than does the United States—294.8 mgA/kgL and 362.5 mgA/kgL, respectively (26, 56). However, animals may have different dosing requirements according to relative size, species, and age, related in part to different pharmacokinetics and pharmacodynamics. In the pork industry, NRDC reports that the United States devotes 338 mg antibiotic/kg pork (mgA/kgP) of MIA to pigs compared with 183 mgA/kgP sold in the United Kingdom and only 44 mgA/kgP in the Netherlands and Denmark (55).

ECONOMIC MODEL OF EXTERNALITIES

AMR represents what economists call a negative externality; i.e., it is a side effect of AMU that affects all members of society without being reflected in the market price of antimicrobials (2, 29). To guide public policy on AMU, it is crucial to evaluate the magnitude of this externality, but, to our knowledge, no studies to date have estimated the externality costs of AMR resulting from AMU in animals. We combine an economic model of the cost of resistance for humans with an evolutionary model of resistance dynamics to antimicrobials to capture the externalities of AMR. For detailed derivations, we refer the reader to an online technical note (27).

Model Setup

We consider a model in which there are two separate pools of pathogens, i.e., a human and a food animal pool, labeled by subscripts h and a, between which diffusion of pathogens occurs in line with the pathways described in the section titled The Fraction of AMR in Humans Attributable to Animal Agriculture. In our context, taking the overall prevalence of pathogens in each pool as given is a reasonable simplifying assumption and allows us to focus on resistance rates of pathogens in each pool, denoted by x_h and x_a.

Food animal pool. Consider first the pathogen pool among food animals and assume that an amount m_a of antimicrobials is applied each period, creating selective pressure s_a per unit on the fraction $(1 - x_a)$ of nonresistant pathogens in the pool, which creates a force that increases resistance. We denote the total effective exposure by $e_a = m_a \times s_a$. Conversely, assume that the trait that confers resistance carries a fitness cost f_a on the fraction x_a of resistant pathogens when no antimicrobial is administered. Given the two opposing forces, the change in the resistance rate of pathogens in the food animal pool is given by

$$\dot{x}_{\mathrm{a}} = (1 - x_a) \times [e_a - f_a \cdot x_a].$$

We focus on steady states of the system to keep our analysis as clear and tractable as possible; i.e., we assume that the resistance rates have converged to the level at which they would arrive if the environment and the input of antimicrobials were held constant for an extended period of time so that $\dot{x}_a = 0$.

If the fitness cost of resistance is less than the effective exposure ($f_a \leq e_a$), then resistant pathogens win out and the system converges toward full resistance so that $x_a = 1$ in the long run. However, if the fitness cost surpasses the effective exposure, then resistance converges to

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$x_a = e_a/f_a < 1$. This is the case in the example data shown next. Resistance is then linear in the effective exposure e_a of the food animal pool and by implication, for given s_a, in the amount of antimicrobial applied, m_a.

Human pool. Let us next consider the resistance rate x_h in the pathogen pool of humans. As in the food animal pool, the human pool experiences effective exposure e_h to antimicrobials given to humans, and resistance carries a fitness cost f_h. In addition, pathogens from the food animal pool diffuse into the human pool at rate d, and a fraction x_a of these pathogens is resistant. The change in the overall resistance rate of pathogens in the human pool thus contains an extra term,

$$\dot{x}_h = (1 - x_h) \times [e_h - f_h \times x_h] + d \times [x_a - x_h].$$

To better relate our model to the data, let us separately denote the fraction of resistant pathogens in the human pool that originates directly from the food animal pool by y_h, which satisfies by definition $y_h \leq x_h$. This fraction is driven solely by the fitness cost and the diffusion dynamics,

$$\dot{y}_h = -(1 - x_h) \times f_h \times y_h + d \times [x_a - y_h].$$

Focusing on steady states with $\dot{x} = \dot{y} = 0$ allows us to solve the resulting two steady-state equations for the normalized diffusion and exposure rates d/f_h and e_h/f_h as a function of the observed levels of x_a, x_h, and y_h. We can then apply the implicit function theorem to the system of steady-state equations to determine the marginal effect of greater resistance among food animals on the resistance rate among humans,

$$\frac{dx_h}{dx_a} = \frac{y_h}{x_a} \times \frac{x_h - y_h}{x_a - y_h},$$

and by implication the marginal effect of antimicrobial application in the food animal pool for resistance among humans,

$$\frac{dx_h}{dm_a} = \frac{s_a}{f_a} \times \frac{dx_h}{dx_a} = \frac{s_a}{f_a} \times \frac{y_h}{x_a} \times \frac{x_h - y_h}{x_a - y_h}.$$

Externality cost of resistance. Denote by C the excess cost of resistant human infections over susceptible infections and by D the disease burden among humans, captured as cases per year, a fraction x_h of which are resistant. Then the total human welfare loss from AMR is given by

$$W = -C \times D \times x_h.$$

The human welfare effect of greater AMR in the animal pool is given by

$$\frac{dW}{dx_a} = -C \times D \times \frac{dx_h}{dx_a}.$$

The negative social externalities from the use of antimicrobials m_a in the food animal sector can be captured by the marginal effect

$$\frac{dW}{dm_a} = -C \times D \times \frac{dx_h}{dm_a}.$$

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Table 1 Input parameters for externality model

Description	Variable	Value
Excess dollar cost per FR human *Campylobacter* infection	C	$1,961 (50)
Number of human *Campylobacter* infections administered FQ	D	94,462 (11)
Fraction of human *Campylobacter* infections with FR	x_b	18% (6)
Fraction of human *Campylobacter* infections attributable to chickens	Y	54% (6, 11)
Fraction of FR *Campylobacter* isolates in retail chickens	x_a	24% (11)
Active enrofloxacin applied to chickens	m_a	6,786 kg (39, 41, 52)

Note: Parameters specific to *Campylobacter* infections, fluoroquinolone resistance (FR), and fluoroquinolone (FQ) use in broiler chickens are extracted from US reports and scientific manuscripts.

Parameterization

We parameterize our model to capture how fluoroquinolone application to broiler chickens (hereafter, chickens) affected the resistance of *Campylobacter* in humans using 1999 data, i.e., prior to the phasing out of fluoroquinolone in chicken production in the United States. The Center for Veterinary Medicine proposed the withdrawal of fluoroquinolone in poultry water in 2000 after an FDA risk analysis determined that the use of fluoroquinolone in poultry caused the development of FR-*Campylobacter* infections in humans (11). The FDA's final decision to withdraw approval of enrofloxacin for use in poultry became effective in 2005 (9).

The input parameters for our model are summarized in **Table 1**. The excess dollar cost per FR human infection (C) was extracted from Thorpe et al. (50) and estimated as the incremental expense that AMR adds to treating a bacterial infection (excluding urinary tract infections) in the United States, deflated from 2014 to 1999 using the gross domestic product deflator for consistency with Thorpe et al. An FDA risk analysis published in 2000 reports 1.6 million human *Campylobacter* cases in 1999 (p. 20), of which 856,000 were attributable to chickens (p. 21), yielding a fraction $y = 54\%$. Furthermore, 50,500 of the chicken-attributable cases were administered fluoroquinolone (p. 21). Assuming the same proportion in all human cases, we extrapolate that $D =$ 94,500 *Campylobacter* patients were administered fluoroquinolone. The fraction x_b of *Campylobacter* infections in humans with FR was obtained from the 1999 National Antimicrobial Resistance Monitoring System (NARMS) report (6). The fraction x_a of FR-*Campylobacter* isolates in retail chickens was extracted from Section V.B of the FDA risk analysis (11).

The total amount of enrofloxacin administered to chickens was obtained by multiplying the number of chickens who received Baytril for metaphylaxis in 1999 (a range of 93.5 million to 136 million as estimated by the FDA), the dosage of 25–50 mg/L enrofloxacin in drinking water, an average daily water intake of growing chickens of 0.143 L, and the dosing period of 3–7 days. The daily water intake was obtained by multiplying the mean age of broiler chickens of 27 days (given that they were slaughtered at 8 weeks with a 2-day withdrawal period for enrofloxacin administration) with a water intake of 5.28 mL per day of age (39, 41, 52). Because the total amount of enrofloxacin administered to chickens enters our externality estimate in the denominator (via the parameter $s_a/f_a = x_a/m_a$), lower amounts of kg used led to higher externality estimates per kg. For our baseline analysis, we thus conservatively employed the high point of the ranges we listed and performed robustness analyses on the implications of using lower values for the AMU data.

Before reporting our results, let us note three caveats to our analysis. First, our data relies on a number of parameter estimates, and of course our results are only as reliable as our inputs. However, given the simplicity of our formulas, it is easy to conduct robustness exercises by varying the parameters. A spreadsheet that the reader can employ to perform robustness analysis is available online (**http://www.korinek.com/AMR**). Second, our model evaluation assumed that the 1999

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data reflected a steady state; this assumption made the analysis significantly more transparent but may have biased our externality estimates downward if in fact resistance rates had continued to climb in the absence of action. Third, our externality estimate cannot be used directly as a corrective tax on AMU in animal agriculture (in the spirit of a Pigouvian tax in economics) because imposing the tax would likely reduce AMU and alter the steady state and the magnitude of the associated externality.

Results

Our main results can be summarized as follows. First, the total excess human cost from FR-*Campylobacter* infections was US$33 million in 1999, of which US$18 million was attributable to chickens. Second, an additional percentage point of FR among chickens would have generated, at the margin, an extra 0.23 percentage points resistance among humans and US$435,000 in extra social costs from treating resistant infections in humans. Third, an additional kilogram of enrofloxacin administered to chickens imposed an externality cost of about US$1,500 on human society, which translated into a 7-cent social cost per chicken just from FR-*Campylobacter* alone. This externality represented a cost on society that was not captured in the price of either the antimicrobial or the chickens sold in the marketplace and, because of the nature of externalities, may have led to overuse of fluoroquinolone in broiler chickens compared with an amount that was desirable from a societal perspective.

For robustness, we analyze the implications of using estimates on the use of enrofloxacin that are informed by the lower ranges listed in the parameterization above. For example, if we employ the estimate of 3.5 million chickens to which enrofloxacin was administered, then the total amount of enrofloxacin used was 4,665 kg, and our externality estimate is about US$2,200 per kilogram used.

DISCUSSION

Preventing unnecessary AMU in animal production is frequently cited as a key strategy for curbing AMR, but the potential human health costs of AMU in animal production have not previously been quantified. We have reviewed the existing literature and have proposed an evolutionary and economic model of resistance dynamics and the resulting externalities to quantify the costs of AMU in animal production on AMR in humans.

As a proof of concept, we applied this model to estimate the excess costs borne by US society as a result of using fluoroquinolones in broiler chicken production in 1999. The introduction of enrofloxacin to US broiler chickens was a unique, landmark case that provided critical insights into the potential downsides of AMU in animal production. First, this antimicrobial was introduced to poultry production during a time when the FDA and the CDC actively monitored AMR in *Campylobacter* from poultry products and human infections. Second, campylobacteriosis in the United States was attributable largely to poultry products. Third, the FDA could estimate enrofloxacin sales in US poultry production. All these factors enabled the FDA and the CDC to recognize a causal relationship between introduction of enrofloxacin for use in broiler chickens and FR-campylobacteriosis in humans. These factors also made this an excellent test case for our externalities approach. However, *Campylobacter* is just one of many zoonotic pathogens under the selection of AMU in food animals. Likewise, fluoroquinolones are just one of many antimicrobial classes that have been used and potentially overused in food animal production since the 1940s.

The FDA has taken several important steps since the late 1990s to reduce the public health risks associated with AMU in food animals. Guidance for Industry (GFI) 152 laid out industry guidelines for assessing AMR-related human health risks before new antimicrobials could be

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introduced to food animal production (12). While GFI 152 substantially increased requirements for new antimicrobials for food animal production, it was not applied to previously approved antimicrobials. Therefore, the FDA subsequently began a series of steps to restrict some of the antimicrobials most important to human medicine, including prohibitions on extralabel uses of fluoroquinolones and cephalosporins and eventually the prohibition of fluoroquinolone use in broiler chicken production. In 2013, the FDA initiated a successful voluntary program to eliminate antimicrobial growth promotion claims, effectively making this use illegal. Finally, in 2015, the FDA implemented the Veterinary Feed Directive (VFD) amendment, which required a veterinary prescription to administer antimicrobials in feed. Together, these steps have likely decreased the potential negative human health consequences of AMU in food animals. (For further descriptions of FDA policies for AMR guidance, see **Supplemental Discussion 5**.) However, the FDA has not eliminated routine AMU in US food animals. In 2017, more than 5.5 million kg of MIAs were sold for use in US food animal production. The vast majority of these drugs were tetracyclines administered to pigs and cattle as feed supplements.

Supplemental Material >

Despite calls by global leaders to decrease AMU in food animals, projections indicate that AMU in food animal production will increase substantially in LMICs over the next two decades (54). These projections are founded on the observation that economic development leads to more meat consumption, which drives the industrialization of food animal production and, in turn, drives more antimicrobial consumption. While the US model for industrialized food animal production has been replicated around the world, the FDA's nuanced approach to restricting some antimicrobials while allowing others to be used extensively has not. Instead, it appears that antimicrobials from across the spectrum of medical importance are used routinely in LMICs (54). The potential for harm from nonjudicious AMU in food animals may be greatest among LMICs, where poor environmental controls and weak food safety regulations facilitate the transmission of bacteria between food animals and humans. LMICs also have fewer resources to detect and address extensively resistant zoonotic infections.

We intend the approach presented in this article to serve as a foundation for future analyses to quantify the external costs associated with AMU in food animal production, including with resistance to other antimicrobials and across other pathogens, other livestock species, and other countries or contexts. Externalities are, by definition, not currently reflected in the cost of antimicrobials used in food animal production and may thus provide incentives for overuse. We hope that better understanding of the external costs of AMU in food animals will help to guide policy decisions aimed to balance the important societal functions of food animal production with the risks of AMR to society.

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AUTHOR CONTRIBUTIONS

All authors reviewed and edited all sections of the article. G.K.I. and P.R.R. jointly wrote the first draft of the manuscript. A.K. developed the externalities model of the section titled Economic Model of Externalities. A.D.S. convened our research group and secured seed funding. C.D.H. developed the concept of the article and guided the writing process.

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