



THE FRANZ EDELMAN AWARD
Achievement in Operations Research

Quantifying Human Health Risks from Animal Antimicrobials

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In 1969, the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine in the United Kingdom warned that uncontrolled use of similar antimicrobials in humans and food animals might promote the emergence of resistant strains of foodborne bacteria that could endanger human health and compromise the effectiveness of antimicrobial therapies in human patients (Swann 1969). The Animal Health Institute (AHI) and its member companies collaborated with Cox Associates, an operations research consulting company, to develop and apply new, practical, quantitative risk assessment (QRA) modeling methods to assess the previously impossible-to-quantify risks (and benefits) to human health from continued use of animal antimicrobials. We came to some surprising conclusions that were robust to many uncertainties. Among these were that antimicrobials that benefit animal health may benefit human health, while regulatory interventions that seek to reduce antimicrobial resistance in animals may unintentionally increase illness rates (and hence antimicrobial use and resistance rates) in humans. These new QRA models and methods enable industry and regulatory decision makers to quantify and compare the probable human health consequences of alternative animal antimicrobial use plans and to design more effective approaches to protect human and animal health.

Key words: decision analysis; risk; health care; epidemiology.

For more than half a century, the agriculture industry has used antimicrobials to prevent bacterial diseases and to promote healthy growth in food animals, such as cattle, poultry, and pigs. Natural selection favors the bacteria in the intestines of these food animals that resist these antimicrobials. Levels of resistance found in practice vary widely both among specific antimicrobial-bacterium (drug-bug) pairs and across countries.

In the United States, the Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA) must decide what uses of animal antimicrobials to approve and for what conditions of use. Growers typically use animal antimicrobials as feed

additives, mixing them into feed or water at low (subtherapeutic) doses to prevent illness or promote healthy growth or to treat and cure illnesses, such as *airsacculitis* (a fatal respiratory disease of chickens and turkeys) and *necrotic enteritis* (NE, a bacterial disease that causes harmful or fatal lesions in the intestines of poultry). They spend approximately 100 million dollars per year on animal antimicrobials used as feed additives in the United States. The Animal Health Institute (AHI) represents the companies that manufacture and sell animal antibiotics and other medications that veterinarians and food producers use. Both the CVM and the AHI are therefore interested in understanding the potential effects of animal anti-

crobials on animal and human health, including possible risks from the natural selection of resistant strains of bacteria.

Since the 1960s, scientists, political authorities, and activists in the United States and worldwide have become concerned that animal antimicrobial-resistant bacteria from food animals might reach and infect humans—especially, those with weak immune systems—via undercooked meats, cross-contamination of other foods in the kitchen, or other (possibly unknown) environmental pathways, and cause illnesses that would resist treatment with similar or identical human antimicrobials. Such illnesses might last a long time and perhaps even cause death in rare, severe cases. We use the term *treatment failure* to describe an antimicrobial treatment that fails to alleviate symptoms as quickly or completely as it would in normally responsive patients. (Treatment failures can occur for reasons other than antimicrobial resistance, such as a patient's intolerance to an antimicrobial drug.) Because of the possibility of resistance-related treatment failures, many people have proposed banning the use in food animals of those classes of antimicrobials used in human medicine.

Industry stakeholders have been unable to reach consensus on the size of this potential threat and to agree on effective risk-management approaches because they lack empirical data demonstrating a causal relation between animal antimicrobial use and adverse effects on public health. Regulatory scientists have noted that “the debate regarding antimicrobial use in animals and subsequent human health implications has been going on for over 30 years, beginning with the release of the Swann report (Swann 1969) in the United Kingdom. The latest report released by the National Research Council (1998) confirmed that there were substantial information gaps that contribute to the difficulty of assessing potential detrimental effects of antimicrobials in food animals on human health” (McDermott et al. 2002, p. 71). Industry scientists are more blunt: “Even though antibiotics have been fed for nearly 50 years to literally billions of animals, there is still no convincing evidence of unfavorable health effects in humans that can be directly linked to the feeding of subtherapeutic levels of antibiotics to swine or other animals” (Cromwell 2002, p. 7). “There has been renewed concern in recent years

about the use of antibiotics in food animal production and the potential risk it may pose to public health due to transfer of antibiotic resistance factors via the food supply...yet there is still no documented case of human treatment failure due to antibiotic resistant bacteria acquired from USDA (US Department of Agriculture) inspected meat and poultry” (Cummings 2006, p. 209).

A Precautionary Response in Europe

Absence of proof of harm is not proof of absence of harm. Harm to human health that is too small to be detected may still be real. Real or not, suspected harm may be unacceptable to regulatory and political decision makers and their constituents. Indeed, in studies of risk perception and communication, researchers have repeatedly found that public concern is largely associated with nonquantitative aspects of perceived risks, including unfamiliarity, scientifically unknown or uncertain risks, mechanisms or processes that are not understood, involuntary and personally uncontrollable exposures (for example, to resistant bacteria in commercially prepared foods), irreversible effects (such as loss of efficacy of current antimicrobials due to the emergence of antimicrobial resistance) caused by human actions, threats specifically to children, and media attention. The perceived risks to human health from antimicrobial use in food animals satisfy most of these conditions for creating high public concern, regardless of what the quantified risks may be. High public concern can readily translate to outrage and calls for legislative and regulatory action if the public does not perceive human health benefits from animal antimicrobial use and if it perceives continued use of animal antimicrobials as letting companies increase their profits in producing food animals while exposing members of the public to needless health risks.

In 1998, the European Union moved from concern to action, banning five classes of animal antimicrobials used to promote growth and to prevent animal bacterial diseases from further use in food animals. It banned the use of the remaining antimicrobials in 2006. The bans were widely viewed as an application of the *precautionary principle* (Pugh 2002), which may be roughly paraphrased as avoid activities judged to have the potential to cause major, possibly irreversible

harm, even if causality has not been fully established. This approach is often applied to biological hazards that cannot be contained easily.

Advocates hailed the banning as a successful act of “political will” that circumvented the deliberate data collection, rational analysis, and causal modeling typical of quantitative risk assessment (QRA) emphasized in the United States. Many advocates, such as the Union of Concerned Scientists, the Alliance for Prudent Use of Antibiotics (APUA), and the activist coalition Keep Antibiotics Working (KAW), urged the United States (and specifically regulatory decision makers at CVM) to drop reliance on QRA and follow Europe’s example.

Uncertainty Creates a Risk-Management Dilemma

Discontinuing animal antimicrobial use is not necessarily risk free. A year after the 1998 bans in Europe, the authors of a United States National Academy of Sciences (NAS) study of the potential human-health risks and benefits of animal antimicrobials summarized the scientific situation:

The benefit to human health in the proper use of antibiotics in food animals is related to the ability of these drugs to combat infectious bacteria that can be transferred to humans through direct contact with the sick animal, through consumption of food contaminated with pathogens, or through proliferation in the environment (National Academies of Science 1999, p. 73). . . . Some groups have argued for a substantial reduction in the use of antibiotic drugs in food-animal production. Others contend that microbial contamination of animal-food products would increase without the use of these drugs. The following summaries of data and studies suggest that antibiotic use in farm animals is largely beneficial. . . . [But] The risk [of animal-to-human transfer of resistance] is greater than zero, but basically incalculable, and the threat is perceived to be significant. The use of *perceived* here is stressed. The threat might be real, and case studies have shown that the passage of resistant organisms from animals to humans can occur and be perpetuated and amplified through food. The question remains, how likely is that to happen? The answer is not available and can be addressed only with the development of the proper database and effective risk analysis (National Academies of Science 1999, p. 78).

Thus, as of 1999, regulators and public health officials in the United States and in much of the rest of the world outside Europe were in the uncomfortable position of having identified a potential risk to human health of unknown size—a risk that might or might not be real, that had not been quantified, and that had concerned politicians, scientists, medical practitioners, and activists. These concerned groups advocated using the precautionary principle to risk management—to ban first and resolve uncertainties later. At the time, no one knew the consequences of such bans for human health, and health analysts could not easily predict the number of treatment failures the bans would prevent (by reducing resistant bacteria) nor the number of new illnesses they might cause (by no longer reducing susceptible bacteria). In 1999, it was also unclear how existing data could fill in the gaps and inform effective risk-management decision making and policy making (National Academies of Science 1999).

In the absence of data, assumptions were being used to support calls for prompt action. For example, in a paper coauthored by one APUA affiliate, the authors declared that “We will assume that the attributable fraction was 5% If the attributable fraction is 5%, this translates to 22,085 infections, 119 hospitalizations, and 1 death in the United States each year as a result of infection by quinolone-resistant *C. jejuni*” (Barza and Travers 2002, p. S129). Public health officials were soon citing these hypothetical numbers (the authors gave no grounds for assuming a five percent attributable fraction) as quantitative evidence of actual harm to human health from resistance to antimicrobial agents (Angulo et al. 2004, World Health Organization 2003a), without noting that they were unsupported assumptions.

Other groups argued qualitatively toward the same end, for example, asserting that the “FDA has an obligation to regulate virginiamycin (one of the animal antimicrobials banned in Europe in 1998) because there’s a reasonable expectation that its continued use in animals will accelerate the evolution of Synercid-resistant bacteria” (Harder 2002). (Synercid, a human antibiotic, is closely similar to the animal antibiotic virginiamycin.) Authors of popular books and media figures supported the movement to ban animal antimicrobials, for example, through such rhetoric as:

“But given how easily enterococci appeared to pass resistance genes to one another as a general matter and how easily VRE (vancomycin-resistant enterococci) circulated in hospitals, how long would it be before Synercid-resistant VRE was ubiquitous? Before the new miracle drug was dead?” (Shnayerson and Plotkin 2002, p. 119). By 2003, Congress had proposed a Preservation of Antibiotics for Medical Treatment Act reflecting these concerns and assumptions. Although not approved, it was to become a perennial feature of the congressional legislative agenda.

In summary, although people had regularly expressed concerns about the impacts on human health of using antimicrobials on animals since the 1960s, it was not until the late 1990s that the rise of the precautionary principle enabled people to translate these concerns into effective political action in Europe. The 1998 ban of animal antimicrobials in Europe seemed likely to be repeated in the United States and in the rest of the world. Although the bans were not guaranteed to protect human health, the possibility that the continued use of animal antimicrobials was harming human health was widely considered unacceptable. Moreover, European health analysts were slow in studying the empirical effects of the bans—the European Food Safety Authority published the first comprehensive survey results in 2006 (European Food Safety Authority 2006).

Quantifying the Health Effects of Animal Antimicrobials

By 2000, the Animal Health Institute (AHI) made developing methods for sound, reproducible, quantitative assessment of the potential effects of using animal antimicrobials on human health a top scientific and strategic priority. Its goal was to develop an objective, data-driven alternative to the European-style precautionary approach. If such bans increased the rate of animal and human illness, they could backfire, unintentionally harming public health. Although people’s perception of risk may be shaped by qualitative considerations, quantitative impacts of risk-management interventions, for example, the numbers of illnesses and deaths per year caused or prevented, determine their real-world health consequences.

AHI also perceived a strategic issue even larger than its current concerns for the survival of animal

antimicrobial products and companies: the appropriate role of science and data in regulatory decision making. Those following the precautionary principle often pay little attention to the causal relation between actions and their probable consequences. They advocate action even before people collect the relevant data and understand cause-and-effect relations. Science, facts, and data need not play a role in shaping the perceptions, concerns, and intentions of those who propose precautionary actions.

In contrast, rational risk management, that is, making decisions that make preferred outcomes more likely, must be driven by the probable consequences of alternative actions, rather than by the concerns or intentions that motivate them. To obtain good results, rather than only good intentions, AHI believed in developing sound quantitative methods to link the uses of animal antimicrobials to their probable human-health consequences, expressed in quantitative terms, such as excess cases or days of illness prevented per year. AHI tried to develop, apply, and share practical methods of quantitative risk assessment to preserve rational (consequence-driven) decision making (and to sponsor the science and data collection needed to predict the consequences of interventions) in regulatory decision processes. Because regulators made concern-driven precautionary decisions in the absence of data for quantifying the probable consequences of decisions, AHI sought ways to enable rational decision making based on the limited data available.

New Operations Research Models and Methods

In 2000, AHI initiated a multiyear series of projects to apply operations research methods with Cox Associates, an independent operations research modeling and consulting company specializing in quantitative methods for decision and risk analysis. Between 2000 and 2005, AHI and several of its member companies, including Phibro Animal Health Corp, Elanco Animal Health, and Alpharma Inc., supported projects to develop and apply a rapid risk-rating technique to produce reliable quantitative estimates of the impact on human health of using specific animal antimicrobials (Cox 2006).

(1) They sought to develop new methods to quantify the unquantified by using currently available

data to quantify how large the adverse human health effects of continued animal antimicrobial use might be. The new methods had to deal with realistic uncertainties, such as the fact that not all environmental pathways leading from animal antimicrobial uses to resistant infections in human patients are necessarily known.

(2) They tried to identify effective and ineffective risk-management interventions. In addition to investigating the ban and continue-to-use options, they investigated a variety of other options, such as changes in processing, or tracking antimicrobial-exposed flocks and assigning their meat to processes and products that killed all bacteria.

(3) They tried to characterize the remaining uncertainties, determine the robustness of their conclusions, and ascertain the value of information for improving current risk-management decisions by collecting additional data and performing additional controlled experiments to resolve scientific uncertainties.

The only constraints AHI imposed were that the methods developed must be technically sound, independently verifiable and reproducible, practical with the existing data, and, if possible, simple enough to explain to nonspecialists. (Thus, for example, it preferred explicit formulas and calculations to complex simulation models.)

Cox Associates, working with AHI and its members, developed several methods and approaches. The first was a discrete-event stochastic simulation model that tracked estimated microbial loads of the bacterium *Campylobacter*—one of the most common causes of foodborne illnesses—on chickens, chicken carcasses, and chicken servings reaching consumers, that is, from farm to fork (Cox and Popken 2002). A farm-to-fork model includes the processes involved in raising poultry, transporting them to the processing plant, processing them into retail products, transporting them to the retail store, and subsequent kitchen preparation and consumption. At each stage, the simulation model sampled the increase or decrease in microbial load per serving from conditional probability distributions based on available data. Our initial model, implemented in the MATLAB programming environment, provided insight into the overall system dynamics. It predicted that the right-hand tail of the frequency distribution of microbial loads caused most

human illnesses attributable to chickens, implying that the industry should focus its prevention efforts on reducing the small proportion of chickens with unusually high microbial loads.

We gained an unexpected insight from the simulation modeling: that without continued use of antimicrobials, poultry may more often develop diseases that increase random variability in carcass sizes and weights, increasing the right tail of the microbial load frequency distribution (Russell 2003). Abnormally large variability in the carcasses causes mechanical problems during processing (tears and ruptures) that can spread high loads of *Campylobacter* from damaged carcasses to other carcasses. The resulting rightward shift in microbial loads for poultry not fed antimicrobials increases the predicted probability of human illnesses (Figure 1). Similar farm-to-fork simulations implemented in the Ithink continuous simulation system predicted that improvements in poultry processing that reduced overall microbial loads would have a much greater impact on human health than interventions that focused solely on reducing antibiotic resistance among poultry.

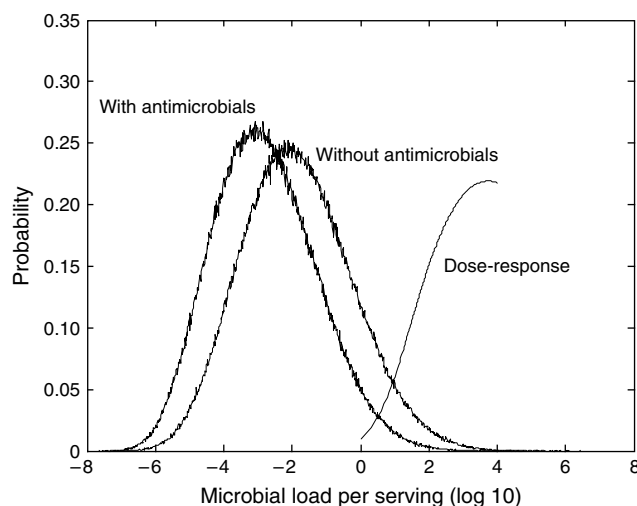


Figure 1: A simulation model generated the microbial load of *Campylobacter* per serving of chicken in situations with and without the application of antimicrobials to chickens during their growth. The dose-response function provides the probability of illness at a given microbial load. By superimposing these functions in the figure above, we illustrate how the rightward shift of the right-hand tail of the microbial load distribution in the absence of antimicrobials significantly increases the incidence of campylobacteriosis.

A limitation of complex simulation models is that one cannot easily manually verify their results without special-purpose software, making simulation insufficiently transparent for use with nonspecialists. We therefore developed a simpler algebraic modeling approach based on steady-state solutions to the systems dynamics model that provided easy-to-communicate bounds on the true but unknown human-health effects of animal antimicrobials (Cox and Popken 2004a). This rapid risk rating technique (RRRT) proved equally useful for quantifying both illnesses prevented and illnesses caused by continued use of animal antimicrobials (Cox et al. 2005, Cox and Popken 2006). Because the animal antimicrobial virginiamycin was attracting attention from regulators and the popular press, with such newspapers as *USA Today* and the *Washington Post* running articles on its potential dangers to human health and with widespread calls for bans, we used virginiamycin as a case study for fully developing and applying the RRRT framework.

To complement the RRRT framework, we also developed a Bayesian Monte Carlo uncertainty analysis model (Cox and Popken 2004b) that used a dynamic model of the emergence of resistance to constrain possible future rates of resistance in human patients to be consistent with observed past rates. The model allowed us to exploit the information that despite decades of exposure to VM, only about one percent of human samples exhibited resistance to its human counterpart, quinupristin-dalfopristin (Synercid). This model predicted that continued use of VM would not cause steady-state levels of resistance in human patients to greatly exceed their low historical levels because model input parameter values that predicted a steep increase in risks also wrongly predicted that it would already have occurred.

Although we tried additional technical methods, for example, Bayesian network and causal graph modeling (Cox 2002), the RRRT framework's relative simplicity and easy verifiability by nonspecialists made it especially effective for obtaining and explaining useful quantitative estimates of human health impacts.

The Rapid Risk Rating Technique (RRRT) Framework

The most important contributions from over six years of quantitative modeling and risk assessment turned

out to be two simple changes in the conceptual framework used to think about antimicrobial risks:

(1) We reframed the problem as one of comparing the probable total consequences to human health of alternate decisions (continue versus discontinue use of animal antimicrobials), rather than one of estimating and judging the acceptability of the currently unknown risks of resistance in human patients caused by the use of animal antimicrobials. The traditional questions that regulators and AHI members had been struggling with were (1) How large is the health risk from the emerging antimicrobial resistance in human populations caused by the continued use of animal antimicrobials? (2) Is this risk acceptable? Assuming that unknown risks are unacceptable (as they are within the prevailing precautionary political and regulatory environment), the only plausible answers to these questions seemed to be Unknown and No, respectively. It seemed that continued use of animal antimicrobials could not be acceptable if only because we had no empirical way to demonstrate their acceptability. We dropped this framing in terms of imponderable quantities in favor of a decision-analytic framing of the problem in which we asked, Would we help or harm human health by discontinuing the use of animal antimicrobials? This emphasis on the probable health consequences of changing the use of animal antimicrobials, rather than on evaluating the acceptability of the current situation, led to a far more tractable and useful analysis.

(2) We reversed the usual farm-to-fork sequence of the traditional risk-assessment modeling approach. Instead of starting with the use of antimicrobials in food animals and attempting to project the (highly uncertain) number of treatment failures that it might eventually cause, we reversed the calculation process. We began with the total number of cases of treatment failures per year actually observed, and then we estimated how this number was changing over time and the maximum fraction of treatment failures that might be prevented by removing animal antimicrobials. By using this clinic-to-farm modeling approach, we were able to estimate all the important model parameters from available data instead of relying on speculative modeling assumptions about microbial growth or decline from stage to stage of the farm-to-fork production process. Most important, we

solved the initially apparently insoluble problem of accounting for unknown biological and environmental pathways connecting animal antimicrobial use to human treatment failures. We started with all cases of treatment failures and calculated the maximum fraction that could plausibly be prevented by ceasing animal antimicrobial uses. We based these calculations largely on genetic biomarker data, especially an *esp* virulence gene that indicated whether cases were human or animal in origin (Cox and Popken 2004a). We could then obtain useful upper bounds on the potential human-health benefits of discontinuing animal antimicrobials, that is, the annual treatment failures and resulting illness-days and lost quality-adjusted life-years (QALYs) that discontinuing their use might prevent. We compared these upper bounds to plausible lower bounds on the human health benefits from continued use (that is, the annual illness cases, illness days, and lost QALYs prevented by continued use). This comparison was tractable with existing data and produced conclusions that were robust to many current scientific uncertainties, including the key uncertainty about the extent to which resistance is transferred from bacteria in food animals to bacteria in human patients.

Applying RRRT Methods to Virginiamycin as a Case Study

Virginiamycin is an antimicrobial used in chickens, cattle, and pigs. *E. faecium* are bacteria commonly found in the intestines of humans and of food animals such as chickens, pigs, and cattle. They normally pose no health risks to hosts with competent immune systems. However, in severely ill human patients with compromised immune systems, such as leukemia, chemotherapy, transplant, and AIDS patients who are typically in intensive care units (ICUs), these normally harmless bacteria can become life-threatening opportunistic infections unless they are controlled successfully with antimicrobials. Vancomycin is the antimicrobial most frequently prescribed to treat *E. faecium* infections, but it can be ineffective against *E. faecium* that express vancomycin-resistance genes. Physicians may then turn to other antimicrobials such as linezolid, daptomycin, and quinupristin-dalfopristin (QD), which are usually highly effective against vancomycin-resistant *E. faecium* (VREF) infections (Critchley et al. 2003).

The US FDA approved the QD compound, Synercid, for use in human patients in late 1999. Farmers in the United States and other countries have used the nearly identical QD compound VM for decades as a growth promoter and to prevent and control bacterial illnesses in farm animals. Poultry often test positive for QD-resistant *E. faecium* (Hershberger et al. 2005), raising the theoretical possibility that use of VM in chickens may compromise QD effectiveness in treating human VREF infections if it promotes the spread of QD-resistant strains from chickens to humans (U.S. Food and Drug Administration 2004). The high prevalence of QD-resistant *E. faecium* in chickens and its low prevalence in humans suggest that transfer from chickens to humans may currently have little or no detectable impact on human health, but the likely future impacts remain uncertain.

If VM used in chickens increases QD-resistant VREF contamination in food products, thus increasing QD-resistant VREF infections in ICU patients with weak immune systems, perhaps following inadequate cooking or handling of hospital food, then more of these patients might have to be treated with alternatives to QD. (We focused on ICU patients because virtually all cases occur within ICU patients.) Linezolid is usually less harsh and at least as effective as QD. However, for patients who do not respond favorably to linezolid (approximately 7.4 percent of VRE patients in a study by Linden 2002) or to other treatment options, such as daptomycin, QD may become the treatment of last resort. QD resistance might then increase the probability of treatment failure for VREF-infected patients prescribed Synercid. Thus, to the extent that QD use in chickens increases QD-resistant VREF infections in ICU patients, it might also increase the number of cases per year that cannot be treated effectively with any currently available antimicrobials, leading to excess mortalities or illness days. We need quantitative risk assessment to determine the number of these treatment failures attributable to QD use in chickens.

Using the RRRT framework for assessing both human health risks and human health benefits, we compare the expected incremental numbers of adverse human health consequences per year caused by the use of an animal antimicrobial (due to increased selection of resistance determinants or resistant bacteria)

to those prevented by the use of an animal antimicrobial (due to reductions in animal illnesses and resulting reductions in microbial loads reaching consumers via meat products). We are justified in using expected events per year to quantify risk for sporadic illnesses that occur independently or with only weak statistical dependence in large populations under the conditions of Poisson or compound Poisson approximations. The top-level formulas are thus as follows, with all quantities representing expected values:

—RISK from continued animal antimicrobial drug use = (preventable resistant illness cases caused per year by continued use) \times (adverse clinical consequences per resistant case).

—BENEFIT from continued animal antimicrobial drug use = (illness cases prevented per year by continued use) \times (adverse clinical consequences avoided per case prevented).

—NET HEALTH IMPACT of continued animal antimicrobial drug use = BENEFIT – RISK = human-health harm prevented – preventable human-health harm caused by continued use. (By preventable, we mean preventable by discontinuing use of the animal antimicrobial drug use. Analogous definitions hold for risk, benefit, and net health impact of introducing a new animal antimicrobial drug.)

In these formulas, all quantities denote expected values. The formulas for human-health RISK and BENEFIT both have the form: (expected cases) \times (expected consequence per case). We justify using these products of expected values to obtain the expected total harm caused or prevented by continued use, respectively, by referring to general results for sums of random numbers of random variables (representing a random number of illnesses, each incurring a random number of QALYs lost, illness-days incurred, and other random quantities).

To estimate RISK and BENEFIT from the data, we further decompose each as a product of more-easily calculated factors (Tables 1 and 2). We calculated the probability of treatment failure as the probability of a conjunction of conditions necessary and sufficient for treatment failure (Table 1): that a patient is infected with high-level vancomycin-resistant *E. faecium* (“VREF_A”) because this is the type of infection for which treatment with Synercid or other alternatives to vancomycin is appropriate; that preferred

alternatives to Synercid, such as linezolid, are not effective; that treatment with Synercid fails because of resistance; and so forth. We justify this product by the fact that a joint probability can always be written as a product of marginal and conditional probabilities, with each probability in a chain of events conditioned on all of its predecessors. We multiply the final probability by the estimated expected consequences of treatment failure.

We made several conservative assumptions (for example, we set fractions equal to one, thereby maximizing estimated risk) when data were missing or inadequate. We reasoned that deliberately biasing the analysis against the conclusion that BENEFIT > RISK by choosing estimates that tend to overestimate risk and underestimate benefits strengthens this conclusion if it still holds. By using more realistic (less biased) estimates of the uncertain quantities when and if we reduce the uncertainties may then tend to further strengthen the conclusion that benefits exceed risks.

We estimated human-health benefits (Table 2) from continued use of VM as follows: If a ban causes an increase ΔF in the fraction of chicken servings that come from ill or high-risk flocks instead of healthy or low-risk flocks, and if each such serving creates an incremental probability ($P^+ - P^-$) of causing human illness (for example, campylobacteriosis), with an average health impact per illness of Q illness-days or QALYs, then the expected human-health impact caused by preventing the increase ΔF in animal illness prevalence is as follows:

$$\text{BENEFIT} = \Delta F \times (P^+ - P^-) \times MNQ$$

illness-days prevented per year, where N = the chicken servings per capita per year, and M = the number of people in the population. We estimated these parameters and their product (Table 2).

To someone managing public health risks, the main question of practical interest is the sign of (BENEFIT – RISK), that is, is the net human-health impact from continued use of an antimicrobial positive or negative? We aimed to provide reusable templates (Tables 1 and 2) easily adapted to other drugs and bugs and populated with plausible parameter values based on currently available data for estimating and comparing

Factor	Values for USA	Data sources
Preventable QD-resistant VREF cases per year		
Expected number of VRE cases/year in ICU population	37,483	AHA (2001), Lawton et al. (2000), NNIS (2001)
Fraction of VRE cases that are of subtype <i>E. faecium</i> (VREF) (Other subtypes of VRE infections are not treated with QD)	0.71, 0.78, 0.95, Median: 0.78	Clark et al. (1993), SNJ (2000)
Fraction of VREF cases with vanA (high-level) resistance, VREF _A (Cases of vanB VREF are not treated with QD)	0.73, 0.79, 0.83 Median: 0.79	Clark et al. (1993), Eliopoulos et al. (1998), Jones et al. (1995)
Fraction of VREF _A cases in hospitals that could have originated from food	<0.17 = proportion not originating in hospitals	Austin et al. (1999), Thal et al. (1998)
Fraction of VREF _A cases from food that might have come from chickens	0 to 0.12 based on genogroup data	Willems et al. (2001, 2000)
Fraction of foodborne VREF _A cases that are also QD-resistant (QD-r VREF _A)	0.011	Cox and Popken (2004b), Eliopoulos et al. (1998), Jones et al. (1999)
Fraction of foodborne QD-r VREF _A cases with QD-resistance caused by VM use in chickens	<1	Upper bound
Preventable resistance fraction = fraction of foodborne QD-r VREF _A cases that might be prevented if VM use in animals ceased	≤1	Upper bound (Cox and Popken 2004b estimate 0.68 within 5 years)
Clinical consequences per QD-resistant VREF case		
Fraction of QD-r VREF _A cases not treated successfully with linezolid or with other non-QD antimicrobials	≤0.074 (0.074 = failure fraction for linezolid alone)	Linden (2002)
Fraction of QD-r VREF _A cases not treated successfully with non-QD antimicrobials that are then prescribed QD and that fail to respond normally	<1	Upper bound
Fraction QD-r VREF _A cases prescribed QD that fail to respond normally because of QD-resistance	0.7	Linden (2002), Moellering et al. (1999)
Increased mortality probability due to QD resistance	0-0.11	Cox and Popken (2004b), Linden et al. (1997)
QALYs lost per nonfatal case	0.04 QALYs, 14.6 illness-days	Cox and Popken (2004b), Webb et al. (2001)
Average QALYs lost per fatal case	21.7	Cox (2005), Webb et al. (2001)
Preventable excess mortalities per year < 0.03 = $37,483 \times 0.78 \times 0.79 \times 0.17 \times 0.12 \times 0.011 \times 0.074 \times 0.7 \times 0.11$	<0.03 mortalities/yr; 0.03/0.11 = 0.27 cases/yr	Product of above lines (using upper bounds)
Preventable excess morbidity QALYs per year = $37,483 \times 0.78 \times 0.79 \times 0.17 \times 0.12 \times 0.011 \times 0.074 \times 0.7 \times (1 - 0.11) \times 0.04$	0.001 QALYs (corresponds to 0.365 illness-days/year)	Cases per year × 0.89 nonfatal × 0.04 QALYs each
Preventable QALYs lost per year = (0.03 × 21.7 QALYs/mortality) + 0.001 from morbidities	<0.65 QALYs	

Table 1: We provide a summary of risk-assessment calculations for the RISK component of the antimicrobial, virginiamycin (Cox and Popken 2004b).

the values of the human-health benefit created (such as lost QALYs prevented per year) and risk caused (such as lost QALYs caused per year) by continued use of VM in chicken flocks.

Our baseline calculations (Tables 1 and 2) indicate that withdrawing VM from use in chickens in the United States would prevent fewer than 0.65 QALYs

lost per year (from less than 0.3 resistant VREF_A cases prevented, even if QD is prescribed in all cases of linezolid failure). This excess-case rate corresponds to 0.03 excess fatalities and 3.5 excess illness-days per year. These plausible upper bounds are small (less than one case per year) because the total number of Synercid treatment failures per year is small. In the

Factor	Value for USA	Data sources
ΔF = fractional change in prevalence of chicken servings from ill or high-risk flocks if current VM use ceases	0.5%	Assumed. It is equal to 1/2 of estimated 1% of flocks currently using virginiamycin
P^- = average probability for the population of illness per serving from animals without disease. Includes indirect effects of cross-contamination of other foods.	1.3E–5	(total <i>C. jejuni</i> illnesses per year) \times (fraction caused by chicken)/(total chicken servings per year)
$P^+ - P^- = (1 + R) \times P^-$ = excess probability of illness per serving from necrotic enteritis positive NE+ flocks	1.2E–4	For linear no-threshold dose-response model, microbial load ratio ≈ 10 (Russell 2003)
M = average number of servings of food commodity ingested per capita per year	38	Cox and Popken (2002) (for fresh chicken)
N = number of people in population	292E6	2003 US census estimate
Q = average human health harm (e.g., days of illness or QALYs lost) per case	6.13 illness days or 0.0043 QALYs lost or 8E–5 fatalities per case	Marano et al. (2000), Buzby et al. (1996)
Risk created by ban = 41,016 illness days/year = 6,691 additional cases/year \times 6.13 days/case.	= 41,016 illness-days or 28 QALYs lost or 0.53 fatalities per year	$[\Delta F(P^+ - P^-)]MNQ$

Table 2: We provide a summary of risk-assessment calculations for the BENEFIT component of the antimicrobial, virginiamycin (Cox 2005).

future, they are expected to decline further as new antimicrobial drugs are substituted for Synercid in human medicine.

More detailed systems-dynamics modeling based on stochastic simulation (Cox and Popken 2004b) shows that resistance to Synercid is also expected to increase little in the future. These calculations enable us to provide a quantitative answer to the rhetorical questions, “How long would it be before Synercid-resistant VRE was ubiquitous? Before the new miracle drug was dead?” (Shnayerson and Plotkin 2002, p. 119). The model-based answers (consistent with experience (Jones et al. 2005)) are that Synercid-resistant (that is, QD-resistant) VRE will never become ubiquitous (the current resistance rate is about one percent or less), and Synercid will not lose its effectiveness because of emerging resistance. Withdrawing virginiamycin from use in animals is therefore expected to have at most a minimal impact on human health due to Synercid resistance.

However, discontinuing the use of VM in chickens could cause over 40,000 excess illness days per year from campylobacteriosis (corresponding to about 6,691 excess cases of campylobacteriosis, 40 of them severe; 0.54 excess deaths; and 28 QALYs lost to illness, based on 0.0043 QALYs per case (Buzby et al. 1996)) for each half-percent increase in such illnesses as necrotic enteritis among chicken flocks. This is a possibility, not a certainty. It is based on two

unproved modeling assumptions: that withdrawing VM will increase animal illness rates, consistent with data from Europe, and that these illness rates will lead to more hazardous meat products with increased microbial loads. Both assumptions are consistent with available data, but neither is certain.

In summary, the baseline expected net human-health impact of withdrawing current VM use under these assumptions would be negative: QALYs caused exceed QALYs prevented by over 40-fold, while the fatality ratio is at least $0.54/0.03 = 18$, and illness-days caused exceed illness-days prevented by over 40,000/3.5 > 10,000-fold. From this perspective, the current information and assumptions incorporated into our calculations (Tables 1 and 2) would not justify banning VM use in chickens but rather suggest that continued use may protect human health. Because of the uncertainties in these model-based calculations, however, sensitivity analysis is essential for these baseline conclusions.

By how much would our numbers have to change to reverse the conclusion that a VM withdrawal would create more cases of campylobacteriosis per year (baseline estimate = 6,691) than the number of QD-resistant VREF cases it would prevent (baseline estimate = 0.27)? If we assumed that all VREF_A infections in hospitals come from VM use in chickens (rather than the baseline estimated fraction of $0.17 \times 0.12 = 0.02$, based on the assumptions that nosoco-

mial cases would not be significantly affected by VM use in chickens and that only human cases with genetic types found in chickens could have come from eating chickens), then the estimate of preventable QD-resistant VREF_A cases would increase from its baseline value of 0.27 per year to a revised value of $0.27/(0.17 \times 0.12) = 13.2$ cases per year. If, in addition, linezolid and other alternatives to Synercid (QD) were to be withdrawn from the market, or if complete resistance to them emerged, then the cases per year could increase further, to $(13.2)/(0.074) = 178.4$. Finally, if the fraction of chicken-derived VREF_A cases that have QD-resistance were also increased by an order of magnitude, from 0.011 to 0.11, then the new estimated number of cases per year, 1,784, would be much closer to the estimated number of prevented campylobacteriosis cases per year, 6,691. (Differences in QALYs per case between these two illnesses reduce the differences in their public health impacts; thus, the order-of-magnitude comparisons of cases per year are only a rough guide.)

More generally, our organization of the calculations as a base number (37,483 VRE cases per year) multiplied by several fractions that are all between zero and one facilitates sensitivity analyses. Increasing any of these fractions (or any two of them, or even any three of them) to their logically maximum possible values of one would not increase the baseline estimate of preventable QD-resistant VREF_A cases per year above the estimated preventable campylobacteriosis cases per year, 6,691. Thus, despite the uncertainties in the analysis, this major comparative conclusion seems robust to uncertainties or changes in any single assumption or any small (less than four) set of assumptions (Table 1). By contrast, we need only to change ΔF or $P^+ - P^-$ to zero to reduce estimated human-health benefits from continued use to zero (Table 2). Conversely, if animal-illness rates were to increase sharply in the United States following a ban on VM and other growth promoters, predicted human-health harm would increase proportionally to ΔF , and the benefits (avoided human-health harm) for an assumed ΔF of 0.005 increase in NE^+ flocks might be too small.

Thus, we should view our estimates of the human-health risk and benefits as uncertain estimates (we intended them to be too high for risks and too low for

benefits, to reduce a decision-relevant difference that is already large). They may change as more scientific information about the microbial load and human-risk impacts of VM withdrawal become available. While the baseline analysis strongly suggests that withdrawing VM is likely to cause more human-health harm than it prevents, uncertainty about the size of the product $\Delta F \times (P^+ - P^-)$ precludes a deterministic conclusion. However, our analysis shows that, based on current information, withdrawing VM now would not be a smart bet for improving human health (and might impair it). There is high decision-analytic value-of-information to finding out more, especially about ΔF and $(P^+ - P^-)$, before implementing a ban, as the current situation shows small possible health gains (less than one case per year prevented) and much larger possible health harm.

In addition to the direct effects on microbial loads and resistance fractions of pathogens reaching consumers, a ban on animal antimicrobials could have indirect effects that would depend on how farmers and physicians adapted to the ban, and whether resistance was transmitted via pathways not addressed in the model. The following are examples of such considerations:

—After the ban on animal antimicrobial growth promoters in Europe, the therapeutic use of other animal antimicrobials to treat animal diseases increased significantly (Casewell et al. 2003). Withdrawing multiple antimicrobials could increase the number of ill flocks (ΔF in the model) by more than the sum of the increases if each one alone were withdrawn, as compensation with others would then not be possible.

—A failure to use animal antimicrobials may increase multiple animal illnesses, increasing ΔF beyond the values we have considered. Thus, if we are considering other pathogens, we might find that human-health benefits from continued use of animal antimicrobials would increase significantly.

—If a ban on VM increases the number of campylobacteriosis cases per year, some of these cases are likely to receive empiric treatment with ciprofloxacin or macrolide antimicrobials. Preventing these cases would remove the need for using these human antimicrobial prescriptions, reducing the corresponding selection pressures for resistance in human pathogens and commensals.

—A common concern is that the resistance fraction may increase over time unless we curb the use of animal antimicrobials. However, biomathematical modeling suggests that, at least for antimicrobials like VM that have been used for several decades in food animals without leading to high levels of resistance in people, an outbreak resistance in the future caused by continued use is very unlikely (Cox and Popken 2004a).

—For simplicity, we have ignored how the timing of a ban affects human health: we have considered only the new levels that will eventually be reached. European experience suggests that the hypothesized health benefits to human patients from banning animal antimicrobials may take longer than five years to materialize, while increases in animal pathogen loads, and possibly in human illnesses, may be much more immediate (Eurosurveillance 2005). If so, a model that considers the timing of impacts might demonstrate further increases in the BENEFIT:RISK ratio for continued use of animal antimicrobials.

In this case study, we focused on QD-resistant VREF_A and campylobacter illnesses transmitted via chicken servings. By including other considerations and extending our study to other pathogens and animals, we might strengthen the conclusion that the risks to human health from withdrawing animal antimicrobials could significantly outweigh the potential benefits to human health.

Implementation and Impact

AHI and its member companies believe that the RRRT work showed a new, constructive way to quantify the previously unquantifiable impacts of animal antibiotic use on human health (National Academies of Science 1999) by using all the available relevant scientific data (mainly epidemiological and molecular biological data) and by making conservative bounding assumptions to bridge data gaps. For example, Willems et al. (2001) concluded that hospital epidemics of vancomycin-resistant *E. faecium* (VREF) on three continents were caused by a genetically distinct subpopulation (carrying the *esp* gene) rarely found in animals or healthy members of the community. Analysts can use such information directly in the RRRT framework to quantify the fraction of cases

that might come from animals. With the RRRT framework, they do not have to make unverified assumptions about the myriad possible (and perhaps largely unknown) environmental and ecological pathways leading from the use of antimicrobials in food animals to antimicrobial-resistant cases and treatment failures in human beings. By starting with a plausible upper-bound estimate of total preventable treatment failures, they can use the RRRT to account for all the pathways leading to them. Finally, the RRRT framework provided the first constructive approach for quantitatively comparing potential human-health benefits of animal antimicrobial use to potential human-health harm. Not only for VM, but for other important classes of antimicrobials, such as fluoroquinolones and macrolides, Cox (2006) found that the potential benefits of continued use might exceed the potential risks by orders of magnitude.

Incorporating New Ideas into Company Thinking

We implemented these methods and introduced our ideas between 2001 and 2005. First, Cox Associates worked directly with AHI member companies, such as Elanco Animal Health and Phibro Animal Health Corporation, to implement the RRRT framework for their products, such as VM (for Phibro) and Tylosin (for Elanco). Company scientists participated in the work and described the RRRT framework, methods, and calculations in top-level executive meetings and in risk-analysis workshops to train company scientists and representatives in markets inside and outside North America. They also presented the RRRT framework and ideas in national and international professional meetings (Shryock 2003) and used them in their own scientific work and policy analyses (Bafundo 2004, Bafundo and Cox 2002, Cervantes 2005).

From AHI's standpoint, we achieved its top-priority strategic goal of finding a way to get solid science, data, and numbers back into risk-management deliberations in a way that its members understood, valued, and used.

Communication with Regulators and Public Health Organizations

Cox Associates and AHI member companies gave presentations on the RRRT methods and calculations in meetings with regulators, in particular, the FDA's

Center for Veterinary Medicine (FDA-CVM), and to national and international regulatory and public health bodies. The World Health Organization (WHO) and other international health agencies cited the RRRT framework and our related work in outlining the scientific background for developing approaches to risk management (World Health Organization 2003b).

AHI and its members thought that by explaining the RRRT framework and its application to VM to regulators, they had helped them to incorporate relevant scientific information, data, and quantitative calculations into applied risk assessment. In 2004, FDA-CVM applied methods similar to ours in a quantitative risk assessment for VM and reached similar conclusions, describing the application in a draft report (U.S. Food and Drug Administration 2004). (The FDA issues draft reports to industry members, scientists, and other stakeholders to obtain comments. For VM, FDA-CVM has not revised or finalized the draft, which stakeholders considered useful and substantially correct as written.) Phibro Animal Health Corp issued a press release (November 30, 2004), summarizing the situation:

In the FDA's draft report, the authors demonstrate that the continued use of virginiamycin—a medicated feed additive manufactured and marketed by Phibro Animal Health—in livestock and poultry feed poses no significant risk to human health. The FDA findings are consistent with extensive analysis conducted on behalf of Phibro Animal Health by Dr. Tony Cox. . . . "We are pleased the FDA has now released this long-awaited virginiamycin risk assessment," said David McBeath, president, Phibro Animal Health. "The findings are consistent with our own conclusions about the historical safety of virginiamycin and its role in protecting both animal and human health" (Institute for Agriculture and Trade Policy 2004).

AHI and its member companies felt that they had advanced the mission of supporting the use of high-quality science, data, and risk assessment in regulatory decision making.

Changing the Intellectual Basis for Quantitative Risk Assessment and Regulation

We presented the main ideas of our work in peer-reviewed papers and at academic and professional conferences. Based on the modeling innovations we developed for the RRRT framework (mainly, the clinic-to-farm approach and the use of a computational

Bayesian analysis of simulation results to assess the stability of QD resistance over time (Cox and Popken 2004b)), the Society for Risk Analysis gave us their Best Paper Awards for 2002 and 2004. Food safety academics and researchers worldwide adopted the RRRT as a useful intellectual framework for assessing food safety and risks (Hurd 2005, Snary et al. 2004).

Protecting Public Health

The most important potential contribution of our work is the most difficult to verify based on the data available today. It is conceivable—and perhaps even likely—that a ban on animal antimicrobials would increase animal illnesses, and thereby human illnesses, and result in increased use of antimicrobials and increased resistance rates in human patients. As data become available from Europe, it becomes increasingly apparent that this distressing theoretical prediction is consistent with experience.

We used conservative bounds to estimate that continued use of animal antimicrobials might prevent at least several thousand excess cases of campylobacteriosis per year in the United States, while causing undetectably low (possibly zero) levels of harm. In practice, Europe's act of precautionary political will banning the use of animal antimicrobials was promptly followed by (1) Large increases in animal morbidity, sometimes lasting for years, due to increased bacterial illnesses, such as necrotic enteritis in chickens and infections with *E. coli* and *Lawsonia intracellularis* in pigs (Casewell et al. 2003); (2) Lasting increases in animal mortality due to increased bacterial infections, for example, a 25 percent increase in pig mortality rates in Denmark that persisted at least through 2005 (KeepMedia 2005); (3) Continuing increases in the rates of human foodborne bacterial illness (*Campylobacter* and foodborne pathogens other than salmonella) throughout much of Europe, although not in every country in every year (European Food Safety Authority 2006, Eurosurveillance 2002, Patrick et al. 2004); and (4) Unexpected increases in antimicrobial resistance rates in clinical isolates from human patients, for example, by several hundred percent in the years following the ban (Hayes and Jensen 2003, Figure 2). Researchers also reported initial decreases in resistant bacteria in healthy animals and humans, as hoped (Wegener

2003), but both human and animal health deteriorated significantly.

If our development of the RRRT framework did nothing more than remind (and enable) decision makers to consider the probable total human-health consequences of alternative decisions, we would have made an important contribution in preventing an overly narrow framing of the problem that would cause decision makers to focus on recommendations designed to reduce resistance in healthy animals, rather than reducing adverse health consequences in sick humans.

Conclusions

As of 2006, a continued reliance on quantitative risk assessment, and new pragmatic methods of making those risk assessments despite sparse data and uncertainties (Bafundo 2004, Cox and Popken 2004a, U.S. Food and Drug Administration 2004), have persuaded US regulatory agencies to resist any bans on antimicrobial growth promoters (AGPs). The differences in health outcomes following the establishment of contrasting policies in the United States and Europe have been dramatic. From 1996 to 2004, the rates of several foodborne illnesses (other than salmonellosis, which was targeted by control programs) increased significantly throughout most of Europe (European Food Safety Authority 2006), for example, by over 20 percent for campylobacteriosis rates in Denmark (Danish Zoonosecenter 2001). Resistance rates to key antimicrobials among bacteria isolated from human patients also more than doubled (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme 2004, Hayes and Jensen 2003). In the United States during the same period, the rates of foodborne bacterial illness fell significantly (by over 30 percent, for campylobacteriosis) (Centers for Disease Control and Prevention 2005, Samuel et al. 2004). Microbial loads of *Campylobacter* in chickens also fell (by perhaps 90 percent between 1995 and 2001, based on a study in Georgia (Stern and Robach 2003)). Resistance rates for key antimicrobials remained fairly stable or declined for domestically acquired campylobacteriosis cases in the United States (Centers for Disease Control and Prevention 2005, Cox and Popken 2004a). Possible contributors to these outcomes

may have included the successful implementation of hazard-analysis-critical-control-point (HACCP) principles, increasing public awareness and education, and perhaps the continued prudent use of key animal antimicrobials.

Cause and effect are notoriously difficult to unravel and interpret correctly in such aggregated historical trend data, so we do not believe that the contrasting histories in Europe and the United States establish that the RRRT-based predictions are necessarily correct. Rather, they demonstrate the potential value of an improved understanding of how animal antimicrobial bans affect animal and human health in analyzing the effects of alternate decisions before implementing AGP bans in the United States.

In conclusion, our analysis suggests that the precautionary-principle approach to regulatory risk management may itself be too risky. The Animal Health Institute and its member companies, such as Alpharma Inc., Phibro Animal Health Corporation, Bayer, and Elanco Animal Health, have helped us develop and apply practical QRA methods for quantifying and comparing the probable consequences of alternative actions to manage risk. These methods work despite our incomplete understanding of the biological and ecological systems involved. They help regulatory officials to identify actions that are likely to benefit human and animal health (and those that are likely to harm it) before they make final decisions. They have used such methods in some recent risk assessments (U.S. Food and Drug Administration 2004), as have increasing numbers of industry and academic analysts. The most important payoff from these methods and their application should be continued improvements in animal and human health.

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Dr. Ken Bafundo, Director, Global Technical Services, Phibro Animal Health Corporation, stated, “Phibro Animal Health Corporation is pleased to support the nomination of Dr. Tony Cox for the Edelman Award. Tony’s risk analysis demonstrated to the

worldwide scientific community that the use of Virginiamycin in animals poses negligible risk to humans and may provide healthier, more wholesome meat products for human consumption. As a result of these findings and their subsequent dissemination, regulatory and scientific bodies around the world have significantly increased the level of scientific rigor applied to risk assessment of all antibiotics used in animals. These developments have been an important part of the process that has demonstrated the safety and supported the future use of Virginiamycin as a meaningful tool in animal production. This, in turn, allows Phibro Animal Health to continue to support and develop products that enhance the health and welfare of domestic animals.”

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