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Potential human health benefits of antibiotics used in food animals: a case study of virginiamycin

Louis Anthony (Tony) Cox Jr.*

Cox Associates and University of Colorado, 503 Franklin Street, Denver, CO, 80218, United States

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Abstract

Risk management of food-animal antibiotics has reached a crucial juncture for public health officials worldwide. While withdrawals of animal antibiotics previously used to control animal bacterial illnesses are being encouraged in many countries, the human health impacts of such withdrawals are only starting to be understood. Increases in animal and human bacterial illness rates and antibiotic resistance levels in humans in Europe despite bans on animal antibiotics there have raised questions about how animal antibiotic use affects human health.

This paper presents a quantitative human health risk and benefits assessment for virginiamycin (VM), a streptogramin antibiotic recommended for withdrawal from use in food animals in several countries. It applies a new quantitative Rapid Risk Rating Technique (RRRT) that estimates and multiplies data-driven exposure, dose–response, and consequence factors, as suggested by WHO (2003) to estimate human health impacts from withdrawing virginiamycin. Increased human health risks from more pathogens reaching consumers if VM use is terminated (6660 estimated excess campylobacteriosis cases per year in the base case) are predicted to far outweigh benefits from reduced streptogramin-resistant vancomycin-resistant *Enterococcus faecium* (VREF) infections in human patients (0.27 estimated excess cases per year in the base case). While lack of information about impacts of VM withdrawal on average human illnesses-per-serving of food animal meat precludes a deterministic conclusion, it appears very probable that such a withdrawal would cause many times more human illnesses than it would prevent. This qualitative conclusion appears to be robust to several scientific and modeling uncertainties.

Keywords: Antimicrobial risk assessment; Virginiamycin; Rapid Risk Rating Technique; Risk-benefit analysis; VREF

1. Introduction: a health risk management dilemma

Enterococcus faecium are commensal bacteria commonly found in the intestines of humans and of food animals, such as chickens, pigs, and cattle. Although they normally pose no health risks when competent immune systems protect their hosts against infections by *E. faecium* and other intestinal bacteria, in severely ill human patients with compromised immune systems, such as leukemia, chemotherapy, transplant, and AIDS patients, these normally harmless bacteria can become life-threatening opportunistic infections unless they are controlled successfully with antibiotics. Vancomycin is the antibiotic most frequently prescribed to treat *E. faecium* infections, but may be ineffective against *E. faecium* that express vancomycin resistance genes. Other antibiotics, such as linezolid, daptomycin, and the streptogramin combination quinupristin–dalfopristin (QD), which are usually highly effective against vancomycin-resistant *E. faecium* (VREF), may then become important treatment options (Critchley et al., 2003). (Note: throughout this paper, underlined or colored words and numbers indicate hyperlinks in the electronic version of the document.) Less effective bacteriostatic agents (e.g., chloramphenicol) are also available, and new antibiotics for treatment of vancomycin-resistant cases (e.g., oritavancin, a glycopeptide, and tigilcycline) are in trial (Linden, 2002).

* Tel.: +1 303 388 1778; fax: +1 303 388 0609.
E-mail address: tony@cox-associates.com.

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A current clinical perspective on VREF infections and resistance is as follows:

"In the United States and Europe, the VanA-resistance phenotype is reported as the most common phenotype. VanA enterococcal isolates exhibit high-level resistance to both vancomycin and teicoplanin, while VanB isolates have variable resistance to vancomycin and remain susceptible to teicoplanin. . . .Enterococcal infections often occur in debilitated patients and as part of polymicrobial infections. . . .The streptogramin combination antibiotic, quinupristin/dalfopristin, is available intravenously for the treatment of *E faecium* infections, but it is not effective against *E faecalis* strains. Linezolid, an oxazolidinone antibiotic, is available orally and intravenously, and it is used to treat infections caused by *E faecium* and *E faecalis* strains. . . .Once VRE vancomycin-resistant enterococci, including *E faecium* and *E faecalis* strains is identified in a medical facility, all clinical enterococcal isolates should be tested for vancomycin resistance." (Donskey and Salata, 2003).

Thus, either QD (formulated as Synercid™ for human medicine) or alternatives, such as daptomycin or linezolid, can be used to treat VREF infections.

If QD used in food animals [formulated as virginiamycin (VM)] increases QD-resistant VREF contamination in meat products, thus increasing QD-resistant VREF infections in immunocompromised ICU patients (perhaps following inadequate cooking or handling of hospital food), then more of these patients might have to be treated with alternatives to QD. Since linezolid is usually less harsh and at least as effective as QD, this is not necessarily undesirable. However, for patients who do not respond favorably to linezolid—approximately 7.4% of VRE patients in a study by Linden et al., 1997—or to other treatment options, such as daptomycin, QD may become the treatment of last resort. QD resistance might then increase the probability of QD treatment failure. Therefore, to the extent that QD use in food animals increases QD-resistant VREF infections in ICU patients, it might also increase the number of cases per year not treated effectively by any currently available antibiotics, leading to excess mortalities or illness-days. Quantitative risk assessment is needed to determine how large is this number of excess treatment failure cases per year. In the absence of quantitative risk assessment, opponents of animal drug use in many countries have urged that VM use in food animals be banned to protect against the perceived but unquantified hypothesized risk to human health (JETACAR, 1999; Wegener et al., 1999; FAAIR, 2002; WHO, 2003).

However, effective public health risk management may not be as simple as banning animal antibiotics, whether in the name of prudence or to avoid perceived potential for unnecessary human health risks. For, continued VM use in food animals may have significant human health benefits, as well as animal health benefits—and the two may be related. VM has long been recognized as effective in preventing and treating bacterial enteritis in swine and poultry (George et al., 1982) and promoting uniformity in weight of animals at slaughter. Veterinary and agricultural experience suggest that more uniform weights and decreases in bacterial illnesses that cause underweight birds at slaughter may be associated with significantly lower loads of microbial pathogens such as *Campylobacter jejuni* and *Salmonella* on processed carcasses (Dawe, 2004). Thus, use of animal antibiotics for prophylaxis and growth promotion may have significant benefits in reducing *C. jejuni* and other pathogens (including *Salmonella*) in processed retail meat. If so, then withdrawing animal antibiotics might increase rates of animal bacterial illness and human food-borne illnesses. Indeed, key animal and human zoonotic bacterial illness rates and antibiotic resistance levels in humans increased in Europe immediately following bans of animal antibiotics (including VM) used as prophylactics and growth promoters (Hayes and Jensen, 2003; Eurosurveillance, 2002), as well as during earlier periods of voluntary restrictions, while declining dramatically in the United States (which continued to use animal antibiotics) over the same period (CDC, 2000, 2003; Stern and Robach, 2003). Such data have been interpreted by some as calling into question long-standing science policy assumptions and assertions that withdrawing animal antibiotics will reduce human illness-days, or, conversely, that continued use of animal antibiotics increases human resistance or illness rates (Cromwell, 2002; Casewell et al., 2003; Phillips et al., 2004). At the same time, many scientists involved in policy making have argued that the animal antibiotic bans in Europe logically should be, and in fact have been, highly successful, e.g., as measured by reductions in resistance in food animals and in healthy humans (e.g., Wegener et al., 1999; Wegener, 2003).

This mixed evidence to date creates a dilemma for public health officials and regulators. Which creates a larger net public health benefit: withdrawing animal antibiotics to reduce selection pressure for resistance in bacteria, or continuing their use to reduce the incidence of food-borne illness and the consequent need to treat some human patients with human antibiotics? The answer is not intuitively obvious. Most previous risk assessments of animal antibiotic use do not illuminate the issue, as they have focused on the risks from resistance without comparing them to the benefits from prevention of illnesses. Moreover, antimicrobial risk assessments are often complex and involve many uncertain data elements, raising questions about whether any quantitative answers that they produce can be clear, robust, and credible enough to be useful to decision makers, while simultaneously taking realistic account of relevant biological processes and their uncertainties (WHO, 2003).

The main purposes of this paper are to offer an analytic strategy for meeting these challenges and to illustrate it by applying it to assess the net human health impacts of the use of QD in food animals in the United States and, for

comparison, in Australia. The analytic framework, which we dub the Rapid Risk Rating Technique (RRRT), is a multiplicative, top-down approach that starts with data on number of clinical cases per year and assesses the estimated fraction that would be prevented by interventions. This approach has been recommended on methodological grounds by several groups (Bailar and Travers 2002; FSRC, 2003; WHO, 2003) but has not previously been applied in detail to assessing the human health benefits and risks of animal antibiotic use.

2. Methods and data: the RRRT framework

2.1. Quantitative health risk and benefit calculations in the RRRT framework

The Rapid Risk Rating Technique (RRRT) approach explained in this section is designed to estimate quantitative impacts of animal antibiotic uses on annual rates of adverse human health effects in a population exposed to bacteria via the food chain and perhaps other paths. These impacts are human health *risks* if they increase the rates of adverse health effects and *benefits* if they reduce them. Both are expressed in units of change in expected numbers of adverse consequences of different severities per capita-year (for individual risks) or per year (for population risks) caused by the risk management option(s) being evaluated. Severities of outcomes may be indicated by severity classes (e.g., mild, moderate, severe, or fatal, as defined by Buzby et al., 1996) or, if desired, by quality-adjusted life-years (QALYs) if the required assumptions are acceptable (Hazen, 2003). While population risks may be further characterized by identifying subpopulations with distinct individual risks from exposure, we will focus on aggregate population risks among ICU patients, as that is the population primarily affected by QD-resistant VREF infections. We also focus on risks from highly (vanA) vancomycin-resistant *E. faecium* ($VREF_A$) infections, both QD-susceptible and QD-resistant, since QD is not active against other VRE, such as *E. faecali*s, while almost all vanB VREF are susceptible to teicoplanin (Eliopoulos, 1998) and not prescribed QD (Murray, 2000). The human populations at risk are all ICU patients infected with $VREF_A$. Health consequences considered include severe illness only, severe illness with treatment failure but not mortality, and fatal cases of $VREF_A$. (Patients without serious illnesses are not normally at risk of $VREF_A$ infections.)

The basic logic of the RRRT approach is to compare the expected incremental numbers of adverse human health consequences per year (a) *caused by* an animal antibiotic use (due to increased selection of resistance determinants and/or resistant bacteria); and (b) *prevented by* the animal antibiotic use (due to reductions in animal illnesses and resulting reductions in microbial loads reaching consumers via meat products). Use of expected number of events per year to quantify risk is justified for sporadic illnesses that occur independently or with only weak statistical dependence in large populations under the conditions of Poisson or compound Poisson approximations (Barbour, 2000). For commensals, the top-level RRRT formulas are as follows:

- RISK from continued animal drug use = (preventable resistant illness cases per year) × (adverse clinical consequences, such as incremental illness-days, per resistant case)
- BENEFIT from continued animal drug use = (prevented illness cases per year) × (adverse clinical consequences avoided per illness case prevented)
- NET HEALTH IMPACT of continued animal drug use = BENEFIT − RISK.

All quantities denote expected values. The formulas for human health RISK and BENEFIT are each of the form "(expected number of cases) × (expected consequence per case). Formal justification for using these products of expected values to obtain the expected total harm caused or prevented by continued use, respectively, follows from general results for sums of random numbers of random variables (representing a random number of illnesses, each incurring a random number of quality-adjusted life-years (QALYs) lost, illness-days incurred, etc.; Feller, 1968). Adverse clinical consequence terms may be expressed as vectors of expected illness-days in each severity class per illness case; expected number of fatalities per illness case, etc.; or, for an aggregate summary, as average QALYs lost per illness case.

To estimate the RISK and BENEFIT formulas from data, each term is decomposed into products of more-easily calculated factors. Fig. 1 shows the structure of such a

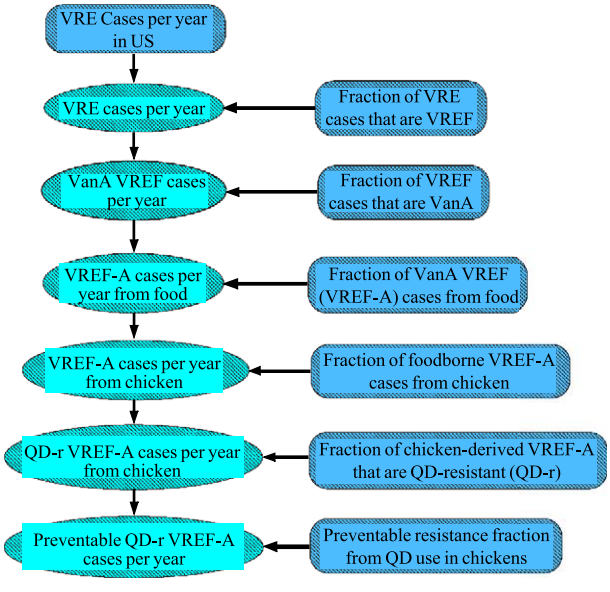

Fig. 1. Calculation logic for preventable resistant illness cases per year.

calculation for the quantity "preventable resistant illness cases per year" appearing in the formula for RISK. The value of each random variable, represented by an elliptical node in this influence diagram, is calculated as the product of the values of the nodes that point into it.

The product form entails no loss of generality or restrictions: *any* joint probability density of values of variables, say, $\Pr(a, b, c, \ldots, y, z)$, can be factored as a product in the form: $\Pr(a)\times\Pr(b\,|\,a)\times\Pr(c\,|\,a, b)\times\ldots\times\Pr(z\,|\,a, b, c, \ldots y)$. The sequence of inputs on the right side of Fig. 1 is such an increasing chain of conditional relations, with each factor being conditioned on all of its predecessors. (Of course, if some of them are irrelevant, then they can be omitted from the conditioning.) Values of the input nodes (i.e., nodes having only outward-pointing arrows) are estimated from available data, as detailed below. Uncertainties in the inputs can be propagated through this diagram using Monte Carlo uncertainty analysis, e.g., using the Analytica™ influence diagram software used to draw it (http://www.lumina.com/). A simpler approach is to use upper-bound estimates for uncertain quantities. The top-down, multiplicative architecture of the model implies that evaluating *any* subset of the input nodes and multiplying them by the first (VRE cases per year in the United States) will give an upper-bound estimate of the final output quantity. Multiplying by further fractions between 0 and 1 can only reduce the estimate further.

The other terms required to calculate the BENEFIT and RISK formulas can be expanded similarly into influence diagrams representing products of factors that are ultimately estimated from data, or sums of such products. Table 1 summarizes the parameters and estimated values used in calculating RISK. Table 2 summarizes the parameters used in calculating BENEFIT. Briefly, if a ban causes an increase ΔF in the fraction of chicken servings from ill [e.g., necrotic-enteritis positive (NE^+)] flocks instead of healthy (NE^-) flocks, and if each such serving has an incremental probability ($P^+ - P^-$) of

Table 1
RRRT risk assessment calculations for VM in chicken

Factor	U.S. values	Data sources
Preventable QD-resistant VREF cases per year		
Expected number of VRE cases per year in ICU population	37,483 (Cox and Popken, 2004a, Table VII, p. 285)	NNIS, 2001; Lawton et al., 2000; AHA, 2001
Fraction of VRE cases that are VREF	0.71, 0.78, 0.95, median: 0.78	SNJ, 2000; Clark et al., 1993; Rice, 2001
Fraction of VREF cases with high-level (VanA) resistance (denoted $VREF_A$)	0.73, 0.79, 0.83, median: 0.79	Eliopoulos et al., 1998; Clark et al., 1993; Jones et al., 1995
Fraction of $VREF_A$ cases in hospitals that could have originated from food	< 0.17 = Proportion not of known nosocomial origin	Austin and Anderson, 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 similarities	Willems et al., 2000; Willems et al., 2001
Fraction of food-borne $VREF_A$ cases that have QD resistance (= QD-r $VREF_A$ cases)	0.011 (Cox and Popken, 2004a, Table VII)	Eliopoulos et al., 1998, Jones et al., 1999
Fraction of food-borne QD-r $VREF_A$ cases with QD resistance caused by QD use in chickens	< 1	Upper-bound
Preventable resistance fraction = fraction of food-borne QD-r $VREF_A$ (i.e., $SREF_A$) cases that might be prevented if QD use in animals ceased	≤ 1	Upper-bound (Cox and Popken, 2004a; estimate 0.68 within 5 years)
Clinical consequences per QD-resistant VREF case		
Fraction of $SREF_A$ (i.e., QD-r $VREF_A$; "S" stands for "streptogramin") cases not treated successfully with linezolid or with other non-QD antibiotics	≤ 0.074 (0.074 = fraction for linezolid alone)	Linden et al., 2002
Fraction of $SREF_A$ cases not treated successfully with non-QD antibiotics that are then prescribed QD and that fail to respond normally	< 1	Upper-bound
Fraction of $SREF_A$ cases prescribed QD that fail to respond normally *because of* the QD resistance	0.7	Linden et al., 2002; Moellering et al., 1999
Increased mortality probability due to QD resistance	0 – 0.11 (see Appendix A)	Linden et al., 1997
QALYs lost per nonfatal case	QALYs, 14.6 illness-days 0.04 (see Appendix A)	Webb et al. 2001
Average QALYs lost per fatal case	21.7 (see Appendix A)	Webb et al. 2001
Preventable excess mortalities per year < 0.03 = $37483 \times 0.78 \times 0.79 \times 0.12 \times 0.011 \times 0.17 \times 0.074 \times \underline{0.7} \times \underline{0.11}$	< 0.03 mortalities/year, from 0.03/0.11 = 0.27 cases/year	Product of above lines (using upper bounds)
Preventable excess morbidity QALYs per year = $37483 \times 0.78 \times 0.79 \times 0.12 \times 0.011 \times 0.17 \times 0.074 \times 0.7 \times 0.89 \times 0.04$	0.001 QALYs (corresponds to 3.5 illness-days/year)	Cases per year × 0.89 nonfatal × <u>0.04</u> QALYs each
Preventable QALYs lost per year = (0.03 × <u>21.7</u> QALYs/mortality) + 0.001 from morbidities	< 0.65 QALYs	

Table 2
Parameters for RRRT baseline benefit assessment for VM

Symbol	Meaning	Baseline value and source
ΔF	Fractional change in prevalence of chicken servings from NE-positive (NE^+) flocks if current VM use ceases	0.5% = assumed baseline value Madsen and Pederson (2000)
P^-	Average probability of illness per serving from animals without disease. Includes indirect effects of cross-contamination of other foods. This probability is an average for the whole population; individual risks may vary.	1.3E–5 = (total *C. jejuni* illnesses per year) × (fraction caused by chicken)/(total chicken servings per year) (Cox and Popken, 2004a)
$P^+ - P^- = (1 + R) * P^-$	Excess probability of illness per serving from NE + flocks (includes cross-contamination effects).	1.2E–4(for linear no-threshold dose–response model, microbial load ratio = 10, from Russell (2003)
M	Average number of servings of food commodity ingested per capita-year	38 FDA-CVM (2001), Cox and Popken (2002) for fresh chicken
N	Number of people in population	292E6 (U.S. Census Bureau)
Q	Average human health harm (e.g., days of illness or QALYs lost) per case. Interpreted as "severity" of a case.	6.13 days (Marano et al., 2000); 0.0043 QALYs, ≥ 8E-5 fatalities per case (Buzby et al., 1996)
Risk created by ban	41,016 = (0.005 × 1.2E-4 × 38 × 292E6 × 6.13 excess illness-days) per year = 6691 additional cases × 6.13 days/case.	$\Delta F(P^+ - P^-)$MNQ = 0.53 fatalities, 28 QALYs, 41,016 illness-days

causing illness (campylobacteriosis), with an average health impact per illness of Q illness-days or QALYs, then the expected human health impact caused by the change in animal illness prevalence is

BENEFIT from animal drug use that prevents ΔF

$$\Delta F = \Delta F(P^+ - P^-)MNQ \text{ illness-days}$$

where N is the average chicken servings per capita-year, and M is the number of people in the population.

To a public health risk manager, the main question of practical interest is the sign of (BENEFIT − RISK); that is, is the net human health impact from continued VM use in animals positive or negative compared to the results of a ban? After addressing this question for the particular case of VM use in chickens, the results will be used as a point of departure for considering how other bacteria, food animals, pathways, and health effects might change the answers. This approach allows rapid qualitative consideration of many other factors that may affect (BENEFIT − RISK) but without greatly changing the key decision-relevant findings.

3. RRRT risk and benefit calculations

Table 1 summarizes the data sources and calculations of the RISK component using the RRRT framework. Throughout, plausible upper bounds (typically, fractions set to 100%) are used where data are missing or inadequate. The derivations of the first six "US Values" of parameters in Table 1 are discussed in greater detail in Cox and Popken, 2004a. Some of the key considerations for populating these data values are as follow (from *ibid*).

The rate of VRE infections in the USA in recent years was estimated from data provided by the CDC National Nosocomial Infections Surveillance (NNIS) System. Antimicrobial resistance data for 1998–2000 were collected from 47 participating hospitals, with a total capacity of approximately 17,766 beds, chosen to approximate the geographic and size makeup of all U.S. hospitals (Lawton et al., 2000). Approximately 677 resistant cases occurred in 2000 out of 2575 isolates tested (NNIS, 2001) from intensive care units. (The updated 2002 NNIS report does not mention Synercid as a treatment for VRE, reflecting the low frequency of its use.) In 2000, there were approximately 983,628 hospital beds in the United States (AHA, 2001). A scale factor of 983,628/17,766 (55.36) multiplied by the number of cases yields approximate nationwide case loads of 37,483 per year, as shown in the first row of Table 1. Uncertainty about the annual value can be approximated by a binomial distribution with $p = 677/2575$ and $n = 2575$, or by a normal approximation to the binomial with mean of $np = 677$, and standard deviation of $\sqrt{np(1-p)} = 22.34$.

According to Rice (2001), approximately 95% of VRE strains in the United States are *E. faecium*. Clark et al. (1993) reported 82 *E. faecium* in 105 VRE isolates (78.1%) from 31 hospitals in 14 states. The State of New Jersey operated a surveillance of VRE blood isolates from 88 hospitals from 1992 to 1998 (SNJ, 2000). During that time, 70.1% of 2339 VRE samples were classified as *E. faecium*. The annual values ranged from 59.5% to 77.5%, without a clear trend up or down. A study of 875 VREF samples was performed on human isolates from hospitals across the United States in 1994–1996 (Eliopoulos et al., 1998). A subset of 352 of the total 875 isolates was identified as the first isolate submitted by any single patient. Seventy-three percent of these samples were vanA and 27% were vanB. *E. faecium* isolates submitted to the CDC from 1988 to 1992 were 83% vanA (Clark et al., 1993). In a 1992 survey of 97 U.S. laboratories, 79% of VREF isolates were vanA (Jones et al., 1995). Using the high and low values reported for the proportion of VRE that are *E. faecium* (VREF), and for the proportion of VREF that are vanA gives a range of $(0.595 \times 0.73 = 0.43)$ to $(0.95 \times 0.83 = 0.79)$ for the proportion of VRE that are vanA VREF. Table 1 takes 0.79 as a point estimate.

Since nosocomial transmission may be viewed as a hospital-specific problem that often can be eliminated by rigorous control measures, Table 1 estimates exogenous (nonnosocomial) cases that could arise from food consumption. Bischoff et al. (1999) found that, of 347 VREF samples taken over a 5-year period at a single institution, only 31 (8.9%) were not likely to have been contracted within the hospital. Austin and Anderson (1999) developed a data-driven simulation model of nosocomial transmission dynamics of VRE in a large Chicago hospital, and estimated that approximately 21% (1 out of 4.81) of cases were not due to transmission from other patients at the hospital, based on assumptions about the probabilities of transmission from health care worker (HCW) to patients and vice versa, staff–patient contact rates (patient contacts per unit time) and the average duration VRE remains transmissible on the hands of HCWs (typically 1 h) and from patients (typically the duration of their stay in the ICU, i.e., days). They conclude that, in the absence of stringent infection control measures, 20% to 25% of cases are exogenous. A study by Thal et al. (1998) found 73 unique strains [via Pulsed Field Gel Electrophoresis (PFGE)] among 379 isolates from 31 facilities in Michigan obtained between 1991 and 1996. In addition, the majority of isolates belonged to the same PFGE strains. They conclude that transmission within and between hospitals is responsible for the majority of cases. The results suggest that perhaps 73/379 or 19.3% of cases are exogenous. These data suggest a plausible range of 0.089 to 0.25 for the proportion of exogenous cases, with a median value of about 0.17 if values greater and less than this are judged about equally likely.

There has been much uncertainty regarding animal sources of QD-resistant VREFs. Willems et al. (2000) used amplified-fragment length polymorphism (AFLP) analysis to clarify VREF sources by analyzing 255 VREF strains isolated from hospitalized patients, nonhospitalized persons, and various animal sources in nine different countries. Four major AFLP genogroups (groups A–D) of vanA VREFs were discriminated. Of the hospitalized patients, 4 had genogroup A strains, 10 had genogroup B strains, while the remaining 73 had genogroup C strains. *Thirty of the 31 chickens had genogroup B strains* as did 6 of 7 turkeys. (One chicken had a genogroup C strain and one turkey had a genogroup A strain.) Group B strains also comprised one or more isolates from other populations, including veal calves and nonhospitalized patients. Group C strains also comprised some isolates from veal calves and all five isolates from cats and dogs. While these data do not determine a precise proportion of vanA VREFs attributable to chicken, they suggest that an attribution of 10 of 87 hospitalized patients (the number with Group B strains) to chicken would be a generous upper bound. Applying a Bayesian approach with a conservative noninformative (uniform) prior to quantify uncertainty regarding the true proportion gives the probability of chicken attribution as a Beta(11,78) distribution, with a mean of $(s+1)/(n+2) = 11/89 \approx 0.12$, based on the highly conservative (i.e., risk-maximizing) assumption that *all* Group B strains found in human patients are due to transfer from chickens. If chickens seldom or never transmit resistant strains to humans however, then the proportion of QD-resistant VREF infections that is attributable to chickens could be as low as zero. A more recent article by Willems et al. (2001) supports the notion that any role of food animals in VREF infections in hospitalized patients is small. One hundred and twenty epidemic and 45 nonepidemic strains of VREF isolates were obtained from hospital patients in the Netherlands, UK, United States, and Australia, and 98 VREF isolates were obtained from Dutch farm animals. (Human strains were regarded as "epidemic" if they had been isolated from the same hospital, if the patients had been in contact during the outbreak period, and if the AFLP patterns showed greater than 90% similarity.) The AFLP analysis technique was used to detect the *esp* virulence gene, which was found in 115 of 120 epidemic isolates, but in *none* of the nonepidemic isolates, and in none of the animal isolates.

In summary, the fraction of human vanA VREF infections that might be due to chickens ranges from 0 to 0.12 as a perhaps extremely conservative plausible upper bound. If it is zero, then no human health risk from vanA VREFs (QD-resistant or not) is caused by use of VM in chickens. To obtain an upper-bound estimate of human heath impacts however, we assume that *all* Group B strains found in humans are directly attributable to chickens, leading to a Beta(11,78) distribution, with a mean of 0.12, as shown in Table 1. This parameter value is used for purposes of contingent risk modeling. All subsequent risk results are contingent on this conservative assumption.

Finally, it is necessary to estimate the fraction of human VREF cases with resistance to streptogramins. In the United States, VREF incidence is relatively high, and VM has also been used extensively for decades. In a study of 875 VREF samples from hospitals across the United States (Eliopoulos et al., 1998), QD inhibited 98.9% of first-isolate strains at $\leq$ 2μg/ml, implying a 1.1% rate of intermediate or higher resistance (four isolates). Another study utilizing 201 VREF isolates from 56 U.S. and Canadian medical centers in 1998 found a QD resistance rate of 1% (2 isolates resistant—none intermediate; Jones et al., 1999). Combining the cases from the Eliopoulos and Jones studies gives a total of 6 resistant isolates from 553 samples, yielding an estimated mean proportion of $p=6/553 \approx 0.011$, as shown in Table 1, with the usual binomial uncertainty distribution.

This completes our summary of data sources and rationales for the values of the first six parameters in Table 1, i.e., the parameters determining the number of "Preventable QD-Resistant VREF Cases Per Year". The human health consequences per case are calculated in the remainder of the table, using parameter values derived and explained in detail in Appendix A.

Table 2 summarizes the calculation of the human health BENEFIT from continued VM use. Key components of these calculations are as follows.

3.1. Calculation of ΔF

Several animal antibiotics, including macrolides and streptogramins (VM), are effective against various bacterial illnesses in chickens, including necrotic enteritis (NE) caused by *Clostridium perfringens* (George et al., 1982; Brennan et al., 2001). Thus, withdrawing these animal antibiotics may increase the fraction of servings from ill flocks and birds, e.g., NE^+ flocks or flocks with other bacterial illnesses having similar impacts on increasing pathogen loads on processed carcasses (e.g., Dawe, 2004).

ΔF denotes the size of this fractional change. To quantify it, we note that NE rates in several European countries increased sharply following bans on VM, macrolides, and other animal antibiotics used as prophylactics and growth promoters, before settling to new, higher levels with increased use of therapeutic drugs (e.g., Lovland and Kaldhusdal, 2001; Madsen and Pederson, 2000; Veterinary Laboratories Agency, 2004). For Denmark, Madsen and Pederson (2000) reported that: "In 1998, necrotic enteritis was diagnosed in 25 out of 1700 Danpo flocks as compared to a few flocks annually before the discontinued use of antibiotic growth promoters." Thus, we estimate that the incidence of NE in Denmark may have increased by about 23/1700 or 1.35 percentage points from 1997 to 1998. However, macrolides (not used much in Denmark), avilamycin (AV), and Zinc Bacitracin have similar effects to VM, and VM accounted for only 0.32 of these drugs by weight in 1996 (DANMAP, 2001). Assuming that a kilogram of each product is similarly effective in preventing NE, the increase in NE incidence attributable to withdrawing VM would be about $\Delta F = 0.32 \times 1.35 = 0.43$ percentage points.

In the United States, where avilamycin is not used, the role of VM would presumably be greater; we round it up to $\Delta F = 0.5\%$. This is the baseline value used in Table 2. However, the true value of ΔF for the United States is quite uncertain and might be much greater than this estimate. For example, in Norway, the NE^+ fraction of flocks increased from 0% before the ban to over 20% in the years following it before finally being brought under control by other antibiotics and countermeasures (Veterinary Laboratories Agency, 2004). To account for this uncertainty, we interpret the results in Table 2 as the human health benefit created (i.e., human health harm prevented) per half-percentage point of NE^+ flocks (or similarly ill flocks) prevented.

3.2. Calculation of P^-

P^- denotes the average risk of a campylobacteriosis illness case per chicken serving from a healthy (e.g., NE^-) flock, including possible effects of cross-contamination of other foods. Since nearly all chicken-borne *C. jejuni* cases currently come from healthy (NE^-) flocks, P^- can be estimated as follows:

P^- = (total chicken-caused cases)/(total servings) = (13.4E-5 reported campylobacteriosis cases per capita-year, from CDC 2003) × (38 assumed cases per reported case, from Mead et al., 1999) × (292E6 people in the United States, from U.S. Census) × (10% estimated fraction of cases from chickens, discussed below) / (292E6 people in the United States) × (38.0 servings per capita-year of "fresh" chicken, from Cox and Popken, 2002) = 1.34E-5 expected campylobacteriosis cases per serving.

Multiplying by the denominator, this corresponds to about (1.34E-05 cases/serving) × (38 servings per capita-year) × (292E6 people in the United States) = 1.487E5 estimated chicken-borne cases per year.

The fraction of total cases caused by eating chicken was estimated as about 57% (FDA-CVM 2001) based on pre-1985 data, but campylobacter counts on processed broiler carcasses have since been reduced by perhaps 90% or more (Stern and Robach, 2003). The true fraction of campylobacteriosis cases caused by eating chicken may have fallen from a pre-1995 value of at most 100% to a current value of at most 10%, assuming a proportional reduction in human risk of chicken-borne campylobacteriosis. The baseline calculations in Table 2 assume a value of 0.10. If a different value is assumed, then the estimated value of P^- will change in proportion.

3.3. Calculation of ($P^+ - P^-$): excess risk of *C. jejuni* cases per serving from AS^+ chickens

We found no direct studies of the human health risks of consuming chicken servings from NE^+ flocks as compared to NE^- flocks. (In the United States, almost all flocks are currently NE^-, making such studies difficult.) However, limited data on another poultry disease, airsacculitis (AS), that may have somewhat similar effects (Dawe, 2004; Lovland and Kaldhusdal, 2001) indicate that airsacculitis-positive (AS^+) flocks are associated with increased *Campylobacter*, *E. coli*, and *Salmonella* on processed carcasses, caused primarily by greater variability in carcass sizes and weakened digestive tracts leading to increased fecal contamination and microbial loads on processed carcasses (Russell, 2003). The mean $\log_{10}$ microbial load of campylobacter colony-forming units (CFUs) before the inside/outside bird wash step of chicken processing for AS^- flocks was 1.09, while the mean for AS^+ flocks was 2.09; thus, the microbial load was about 1 log (10-fold) higher for the AS^+ flocks, although there was considerable flock-to-flock variability (with increases in only three of five replicates). If a linear no-threshold model is used (i.e., human campylobacteriosis risk is proportional to CFUs per

processed carcass) and if the average risk of chicken-borne campylobacteriosis is therefore about 10 times greater for carcasses from NE^+ flocks compared to NE^- flocks (using the microbial load data of Russell, 2003 for AS^+ compared to AS^- flocks as a surrogate for NE) then $(P^+ - P^-) = (10 \times P^- - P^-) = 9 \times P^- = 9 \times 1.34\text{E-}5 = 1.2\text{E-}4$ is the excess individual risk of campylobacteriosis per serving from an NE^+ bird. (If a log-exponential model for chicken-borne campylobacter risk assessments is used to account for variability in chicken-borne exposures to Campylobacter (FDA, 2001), then $(P^+ - P^-) = 138.3 \times P^- = 0.002$; see Cox and Popken, 2005; Appendix A.)

4. Results

4.1. Calculation of human health benefits from continued VM use

Tables 1 and 2 are intended to provide reusable templates, populated with plausible parameter values based on currently available data, for estimating and comparing the values of the human health BENEFIT created (i.e., lost QALYs prevented per year) and RISK caused (i.e., lost QALYs caused per year) by continued use of VM in chicken flocks. For a fractional change $\Delta F = 0.5\%$ of chicken flocks changing from being healthy (e.g., NE^-) to being ill (e.g., NE^+) following a withdrawal of VM, the resulting percentage increase in human campylobacteriosis risks from eating chicken (assuming a directly proportional relation between microbial load of *Campylobacter* at processing and risk of human campylobacteriosis illness) is estimated to be: $(99.5\%) \times 1 + (0.5\%) \times 10 = 104.5\%$ (i.e., 99.5% of chickens would be unaffected and 0.5% would be about 10 times riskier than at present.) This corresponds to an estimated *4.5% increase in chicken-borne campylobacteriosis cases per 0.5% increase in flock illness rates if VM use is withdrawn.* As indicated above, allowing for log-exponential interindividual variability in infectious doses received from a given microbial load at processing, e.g., due to differences in handling and cooking, and as well as in susceptibility, would increase this estimate approximately 14-fold. If the baseline risk is 1.487E6 estimated cases per year in the United States, with 0.10 being caused by chicken-borne campylobacter, as estimated above, then the estimated increase in cases per year from withdrawal of VM would be: $(1.487\text{E}6) \times (0.10) \times (0.045) = 6691$ additional campylobacteriosis cases per year. Of these, only a fraction of about 0.006 are expected to be severe (Buzby et al., 1996), giving an estimate of about $6691 \times 0.006 = 40$ severe campylobacteriosis illness per year. Buzby et al. (Table 2, p. 4) also estimate a fatality rate of at least 200 deaths per 2.5 million cases (and possibly 730 deaths per 2.5 million cases), giving an estimate of at least $6691 \times (200/2.5\text{E}6) = 0.54$ excess deaths.

The baseline calculations in Tables 1 and 2 indicate that withdrawing QD from use in chickens in the United States would prevent not more than 0.65 QALYs lost per year (from less than 0.3 preventable resistance cases. This corresponds to 0.03 fatalities and 3.5 excess illness-days). It would be expected to cause over 40,000 excess illness days per year from campylobacteriosis [corresponding to about 6691 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 NE-positive chicken flocks. Thus, the expected net human health impact of withdrawing current QD 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.

5. Uncertainty and sensitivity analyses

To reverse the conclusion that a VM withdrawal would create more cases of campylobacteriosis per year (baseline estimate = 6691) than the number of QD-resistant VREF cases it would prevent (baseline estimate = 0.27), one might seek to increase the estimated fractions in Table 1. For example, suppose that it were assumed that *all* $VREF_A$ infections in hospitals come from VM use in chickens (rather than the baseline estimated fraction of $0.17 \times 0.12 = 0.02$ in Table 1, based on assumptions that nosocomial 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 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, 1784, would be much closer to the estimated prevented campylobacteriosis cases per year, 6691.

More generally, the calculations in Table 1 are organized as the product of a base number (37,483 VRE cases per year) multiplied by several fractions that are all between 0 and 1. Increasing any of these fractions (or any two of them, or even any three of them) to their logically maximum possible values of 1 would not increase the baseline estimate of preventable QD-resistant $VREF_A$ cases per year above the estimated preventable campylobacteriosis cases per year, 6691. Thus, despite the uncertainties in the analysis, it appears that this major comparative conclusion is robust to

uncertainties or changes in any single assumption, or any small (< 4) set of assumptions, in Table 1. (Differences in QALYs per case between these two illnesses reduce the differences in their public health impacts, as quantified above; thus, the order-of-magnitude comparisons of cases per year are only a rough guide).

By contrast, in Table 2, it is only necessary to change ΔF to 0 or $P^+ - P^-$ to 0 to reduce estimated benefits to 0. We have attempted to choose conservative values of these quantities: $\Delta F = 0.005$ as in Denmark instead of $\Delta F > 0.1$, as in Norway; and $P^+/P^- = 10$ instead of $P^+/P^- = 140$, as estimated for the FDA, 2001 log-exponential model (Cox and Popken, 2005; Appendix A), as well as assuming that only 0.10 of campylobacteriosis cases are caused by chicken, instead of 0.57 as in FDA, 2001. Thus, our estimated benefits may be biased downward by as much as $(0.1/0.005) \times (140/10) \times (0.57/0.10) \approx 1600$ based on these alternative parameter values. However, the true benefits could also be smaller, or even zero if $(\Delta F) \times (P^+ - P^-) = 0$, depending on how animal illness rates and microbial loads would change following a VM withdrawal. If NE were to increase sharply, as in Norway following the ban on QD and other growth promoters, then predicted human health harm would increase proportionally to ΔF, and the benefits (avoided human health harm) estimated in Table 2 for an assumed ΔF of 0.005 increase in NE^+ flocks might be too small. Thus, the human health risk and benefits estimates in Tables 1 and 2 should be viewed as conservative but uncertain estimates (designed to be probably too high for risks and too low for benefits, to reduce a decision-relevant difference that is already large) that 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 far more human health harm than it prevents, scientific uncertainty about the size of the product $(\Delta F) \times (P^+ - P^-)$ precludes a deterministic conclusion.

6. Extensions to cattle and swine

To extend the risk assessment in Table 1 to include cattle and swine, we compare streptogramin resistance levels in VREF isolates from cattle and pigs to those from chickens. Jensen et al. (2002) reported a ratio of streptogramin resistance in isolates from pigs vs. broilers of (0.51/0.67) and a ratio of streptogramin A resistance (which is necessary for QD resistance) of (0.14/0.96). We estimate that the ratio of per-capita consumptions of high-risk (e.g., ground) pork meat to high-risk (e.g., fresh) chicken meat as not more than 0.25. Willems et al. (2000) found that only 4 of 87 (4.6%) hospitalized patients had VREFs from the same genogroup as pig VREF isolates, compared to 12% for chicken VREF in Table 1. Thus, even if all QD-resistant VanA VREF from pigs are attributed to VM use, the total QD-resistant VanA VREF risk to humans from pigs might be only about $(0.51/0.67) \times (0.14/0.96) \times (0.25) \times (4.6/12) = 0.01$ times as great as from chicken (assuming comparable effects of processing and cooking). Similarly, for cattle, Willems et al. (2000) found that, among hospitalized patients, most VREF (84%) belonged to a different genogroup from that in most (70%) veal calf isolates. Assuming that QD-resistant VREF are not more prevalent in beef servings than in chicken or turkey servings (Wegener et al., 1997; Hayes et al., 2003), data on consumption rates of undercooked beef (MRC, 1995) suggest that the human health risk due to beef might be at most about 3% of that from chicken.

In summary, including beef and pork is unlikely to increase estimated human health risk of QD-resistant VanA VREF infections due to VM use in food animals by more than about 4% compared to those estimated for chicken alone. In reality, the severely or critically ill patients at risk may be relatively unlikely to be exposed to QD-resistant VREF in undercooked meat from any of these sources.

7. Comparison to Australia

An advantage of the RRRT framework is that it can readily be applied to estimate risks in one country by adjusting the parameter estimates for another country. To illustrate, the estimated parameter values in Table 1 would be adjusted as follows to estimate VM-associated risks in Australia, a country that has considered banning VM:

- VREF cases per year ≈ 16 instead of $(37{,}483 \times 0.78 \approx 29000$ in the United States), due in part to the smaller population size (data in Cox and Popken, 2004a).
- The fraction of VREF cases that are VanA is only about 0.22 in Australia (Turnidge, 2001) rather than about 0.79 as in the United States, shown in Table 1.
- The observed fraction of QD-resistant cases among VREF cases in humans in Australia is 0 (Turnidge and Bell, 2002), although isolates of *E. faecium* from both pork and poultry in Australia have high levels of streptogramin resistance—81% in retail pig meat and 96.6% in chicken carcasses. Applying a conservative Bayesian approach with a uniform prior (mean = 0.5) to the 0 observed QD resistance rates for humans yields a beta posterior distribution with a mean of approximately 0.009 (Cox and Popken, 2004a). The consumption-weighted average streptogramin resistance among food animal sources (chicken, pork, and beef) exceeds 0.5, suggesting an average food-borne fraction of human VREF cases of less than $0.009/0.5 < 0.02$, which might be compared to 0.17 in Table 1. As this calculation

makes speculative assumptions, it will not be used further.

Holding the other estimated parameters in Table 1 constant, the first two of these adjustments indicate that the current health risks from QD use in food animals are only about $(16/29000) \times (0.22/0.79) = 1.5/10{,}000$ as great as in the United States, and hence are vanishingly small—fewer than one excess case expected per millennium.

8. Discussion

8.1. Comparison to other risk assessment approaches and models

In contrast to farm-to-form models, the RRRT approach developed and applied in this paper makes no attempt to identify explicitly all possible pathways or biological mechanisms leading from VM use in food animals to QD resistance in human $VREF_A$ infections. Rather, it starts with an observed data point (the number of cases per year in the human population) and works backward to calculate an estimated upper bound on the fraction that might be prevented by removing VM uses in food animals. Table 1 summarizes the fractions used in the calculation. Uncertainties about the correct values of these fractions (and about the causal pathways and biological phenomena involved) were handled by an upper-bounding approach and through sensitivity analyses. Similarly, the extent of biases introduced by repeated use of conservative and upper-bound assumptions and/or by possible incorrect assumed values for the model parameters in Table 1 is bounded by the fact that none of the fractions can exceed 1.

Uncertainty about future values of the number of cases per year in the human population is examined in detail in a separate paper (Cox and Popken, 2004b) using a population dynamics model of the emergence of resistance that includes the possibilities of colonization, secondary amplification, and person-to-person spread of resistant *E. faecium*. That analysis concludes that the endemic level of resistance in the human population is extremely unlikely to increase as a result of VM use (as the basic reproductive rate R_0 of resistant VREF is much smaller than 1.) In addition, sensitivity analysis of Table 1 indicates that even increasing the number of $VREF_A$ cases per year and/or the QD resistance rate per case 10-fold would not reverse the main finding that the expected human health benefits from continued VM use are much larger than the expected human health risks.

8.2. Comparison of model predictions to experience

Documented Danish experience following the withdrawal of growth promoters provides an opportunity to compare model-predicted human health impacts to observed data. From 1997 to 1998 (when antimicrobial growth promoters were banned), the number of cases of campylobacteriosis in Denmark increased 26.5%, from 2666 to 3372 (Dansk, 1999), while poultry production in Denmark increased by only about 7.4%. The unaccounted-for increase in cases from 1997 to 1998 $[509 = (26.5\% - 7.4\%) \times 2666]$ is roughly consistent with the previously estimated 1.35% increase in NE-related contamination in Denmark (detailed under Calculation of ΔF above) and baseline estimate of a 4.5% increase in human campylobacteriosis cases per 0.5% increase in animal illness rates: $(0.045) \times (1.35/0.5) \times 2666 = 324$. In addition, Denmark determined the serotypes of campylobacter infecting humans, broilers, cattle, retail poultry, and healthy dogs (Dansk, 1998, 1999). The covariance of serotypes between humans and retail poultry increased from 1997 to 1998, consistent with the hypothesis that increases in campylobacter may have been due to increased contamination from chickens. Finally, the added cases occur in higher age groups, while the campylobacteriosis case rate per 100,000 declined among infants less than 1 year old, consistent with a food source not consumed by infants (e.g., fresh chicken; Dansk, 1999). In summary, while these sources of evidence are only circumstantial and many other possible historical influences may also have had important effects, the observed increases in campylobacteriosis illness rates in Denmark are of the same order of magnitude, although somewhat larger than, the impacts predicted by our baseline model.

8.3. Other considerations and extensions of the RRRT calculations

In addition to direct effects on resistance levels and microbial loads reaching consumers in food servings, withdrawing VM could have important indirect effects that depend in part on human decisions and behaviors as they adapt to the ban and/or that are transmitted via causal pathways other than those addressed in the model. Examples of such additional considerations, with brief comments, are as follows:

- *Antibiotic substitutions.* Following bans on food animal antibiotics used as growth promoters and prophylactics in Europe, therapeutic uses of other animal antibiotics, of greater potential relevance to human health, to treat animals increased significantly (Casewell et al., 2003). By analogy, withdrawing QD use in the United States might cause increases in NE that could be controlled by increasing veterinary prescriptions of other antibiotics. Doing so could increase the human health risks from a VM withdrawal (*ibid*), and the estimated human health benefits from continued use.
- *Other food-borne human pathogens. Salmonella*, *C. perfringens*, and other pathogens, as well as *C. jejuni*,

may be significantly greater in chicken servings from NE^+ compared to NE^- flocks. This would further increase the estimated human health benefits from continued use of animal antibiotics.

- *Other animal illnesses.* Animal bacterial illnesses other than NE might also increase following withdrawal of VM, providing additional benefits from continued use.
- *Coselection and commensals.* Macrolides used in chickens may coselect *E. faecium* that are resistant to streptogramins, although the genes responsible for resistance to streptogramin A are rarely found in animal isolates. Since glycopeptides and linezolid are not used in food animals in the United States, there is no potential for coselection with genes that confer resistance to these two human-use-only antibiotics.
- *Reduced need to treat human patients with antibiotics.* If a ban on VM increases campylobacteriosis cases per year, some of these cases might receive treatment with ciprofloxacin or macrolide antibiotics as empiric treatments. Preventing these cases would remove these human antibiotic prescriptions, potentially reducing selection pressure for resistance in human pathogens and commensals.
- *Emergence of resistance.* A common concern is that the resistance fraction in food animal bacteria may increase in future unless animal antibiotic use is curbed (FAAIR, 2002). However, biomathematical modeling suggests that, at least for antibiotics, such as VM, that have been used for several decades in food animals without producing high levels of resistance in people, an outbreak of high resistance in the future from this source is very unlikely (Cox and Popken, 2004b).
- *Timing:* For simplicity and to be conservative (i.e., maximizing the estimated risk of continued use of the animal antibiotic), the *timing* of human health impacts of a ban has so far been ignored: only the new levels that will eventually be reached have been considered. Evidence from Europe suggests that the hypothesized health benefits to human patients from banning animal antibiotics may take longer than 5 years to materialize (Heuer et al., 2002; Borgen et al., 2000; Iversen et al., 2002), while adverse impacts on increased animal pathogen loads (e.g., Madsen and Pederson, 2000) and possibly on human health (Eurosurveillance, 2002) may be much more immediate. If so, then modeling the timing of impacts might further increase the benefit-to-risk ratio for continued use of animal antibiotics in this example.

In summary, while the analyses in Tables 1 and 2 focused on QD-resistant VanA VREF and on campylobacter illnesses transmitted via chicken servings, other important considerations may tend to strengthen the conclusion that human health risks from withdrawing or restricting QD use in chickens could significantly outweigh potential human health benefits.

Such additional comparisons and information can be included in expanded quantitative human health risk analyses (e.g.,Cox and Popken, 2004b). However, doing so may have limited value from a decision analysis point of view if the main effect is to further strengthen the already strong conclusion from Tables 1 and 2. A key prescriptive principle of value-of-information (VOI) analysis is not to pay for information that does not have the potential to change the risk management decision. By contrast, better information on the extent to which withdrawing animal antibiotics increases animal disease rates and microbial loads in animal carcasses and resulting illness risks to consumers [the size of the $(\Delta F) \times (P^+ - P^-)$ term in the model in Table 2] could be very valuable in reducing uncertainty about the baseline conclusion that continued VM use has human health benefits far larger than its human health risks.

9. Conclusions

This paper has introduced and illustrated an approach for estimating the human health impacts of animal antibiotic uses—the Rapid Risk Rating Technique (RRRT)—that appears to be practical to implement with available data for antibiotics and pathogens of practical interest. Potential human health benefits from discontinuing animal antibiotic uses are estimated by multiplying total clinical case rates by a sequence of fractions estimated from data (or conservatively bounded, e.g., by setting highly uncertain fractions equal to their maximum possible value of 1) to estimate the number of potentially preventable cases and adverse consequences per year. Potential human health risks from discontinuing use are estimated by multiplying the expected increase in food animal illness rates by the estimated increase in human illnesses (and resulting adverse consequences) per year per unit increase in animal illness rates.

The RRRT approach is designed for use in situations in which either (a) qualitative considerations are insufficient to support clear, effective risk management decision making, e.g., because the quantitative size of health risks matters and/or because qualitative assessment suggests that a proposed intervention may cause both human health benefits and human health risks, and it is important to estimate which is larger; or (b) available data and resources are not sufficient to build and validate a more detailed quantitative model, and/or rapid risk rating using RRRT provides a sufficiently clear answer so that more expensive and detailed quantitative estimates are considered unnecessary. The risk and benefit factors estimated in the RRRT framework, e.g., via Tables 1 and 2, are intended to provide the least amount of information that is both necessary and sufficient to estimate and compare quantitative human health risks and benefits from alternative risk management interventions.

We have illustrated the RRRT approach using virginiamycin (VM) in chickens as a case study. The baseline estimates presented in this paper suggest that the human health harm from discontinuing VM use in chickens may substantially exceed the potential human health benefits, even under baseline assumptions that are intended to be fairly conservative. Scientific uncertainties are great enough to preclude available data from proving with certainty which option (i.e., continuing or discontinuing VM use) will create fewer adverse human health impacts. However, the RRRT calculations strongly suggest that continued use of VM would *prevent* at least thousands of times more illness-days (as well as more fatalities and cases) per year than it would *cause*. Thus, any risk management strategies that recommend withdrawing VM use in chickens for precautionary or other motives must be based on principles, assumptions, or data very different from those considered in this paper.

Appendix A. Estimating human health impacts of QD resistance in VREF

VM use in animals can adversely affect human health only if there is a difference in the human health consequences of QD-resistant vs. QD-susceptible strains of VanA VREF, perhaps due to differences in the medical treatment received. This appendix estimates this difference.

A.1. Health consequences of VREF and SREF infections

Fig. A1 illustrates possible health outcomes for QD-susceptible (SUS) and QD-resistant (RES) vanA VREF cases, with their estimated probabilities. Each VanA VREF patient has an initial health state classified as either "severe illness" (but susceptible to QD treatment) or as "QD treatment failure (=not susceptible to effective QD treatment)." Each has a final health outcome of either "Severe" illness (but responded to QD treatment), QD "Treatment failure" (but no fatality), or "Fatality". An initially severely ill vanA VREF-infected patient who does not respond to QD enters the "Treatment Failure" state, from which progression to the "Fatality" state may then occur. Transition from Severe illness to the Treatment Failure state can occur not only if the vanA VREF infection is QD-resistant, but also for reasons such as a patient's intolerance of QD. (These latter could be classified as "unable to treat with QD" rather than as "treatment failures", but the distinction is not needed for quantifying the increase in treatment failures due to resistance.) Transitions to the "Fatality" category can occur from both the severe illness and treatment failure initial categories, but the probability of fatality is higher for treatment failures (0.525 vs. 0.37).

The transition probabilities from Severe Illness to Treatment Failure and from both Severe Illness and Treatment Failure to Fatality are estimated as follows. Lautenbach et al. (1999) reported a 37% VRE-attributable mortality rate among patients with enterococcal bacteremia, 28% of whom were resistant to vancomycin. A case-control study by Edmond et al. (1996) found a mortality rate of 37% (95% CI = 0.1, 0.64) for vancomycin-resistance among cases of enterococcal bacteremia, gives an estimated value of

$$\Pr(\text{fatality}|\text{severe illness and no QD resistance}) = 0.37$$

Linden et al. (1997) found that 5/20 (25%) of cases given QD had VREF-associated mortality while 17/42 (40.5%) controls receiving alternative treatment had VREF-associated mortality. These proportions are borderline statistically significantly different ($p=0.067$ in a two-sided test for difference of proportions, $p=0.034$ for a one-sided test). Their difference of 40.5 – 25 = 15.5% can be used as a plausible conservative estimate of the increase in mortality probability attributable to not being treated successfully

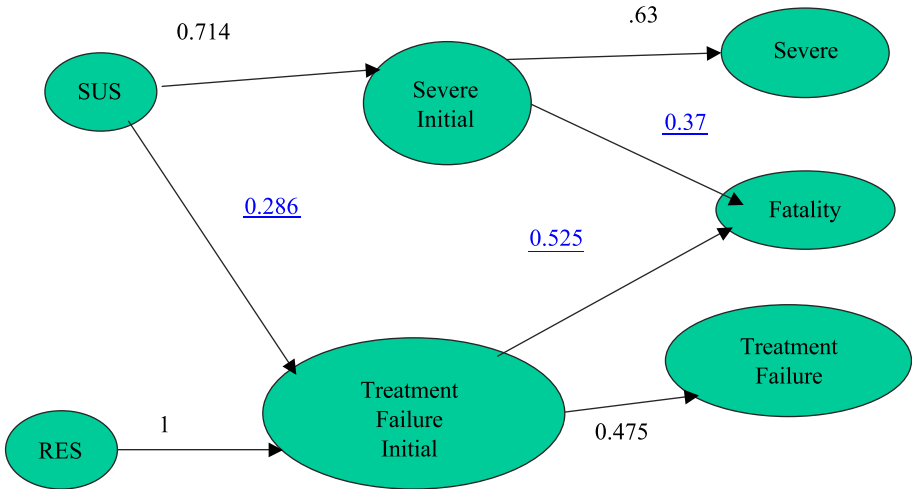

Fig. A1. Outcome probabilities for QD-resistant (RES) and QD-susceptible (SUS) VREF cases.

with QD. (If the true difference is zero, the total risk associated with QD resistance would also be zero.) The estimated fatality probability among Treatment Failure patients is thus

$$\Pr(\text{fatality} \mid \text{QD treatment failure}) = 0.37 + 0.155 = 0.525$$

The probability of treatment failure is defined as 1 among QD-resistant cases:

$$\Pr(\text{QD treatment failure} \mid \text{QD resistance}) = 1$$

However, QD is often not completely effective, even in the absence of resistance. In a recent study, the clinical success rate in the bacteriologically evaluable subset of patients was 70.5% with a 95% confidence interval range of 63.4% to 77.7% (Moellering et al., 1999; Linden, 2002). A fraction of the treatment failures (about 0.009; Cox and Popken, 2004a) were due to resistance and must be subtracted out to get the fraction of failures that are not due to QD-resistance:

$$\Pr(\text{QD treatment failure} \mid \text{QD} - \text{susceptible}) = 1 - 0.705 - 0.009 = 0.2860$$

The final outcome probabilities for QD-resistant and -susceptible infections are computed as follows:

- Pr(severe illness is the final outcome | QD-resistant) = 0 (see Fig. A1).
- Pr(fatality | QD-resistant) = Pr(fatality | QD treatment failure) = 0.525
- Pr(treatment failure but no fatality | QD-resistant) = 1 − 0.525 = 0.475
- Pr(severe illness is the final outcome | QD − suscepti-ble) = Pr(severe illness and successful treatment and no fatality | susceptible) = 1 × (1 − 0.286) × (1− 0.37) = 0.45
- Pr(QD treatment failure but no fatality is final outcome | QD-susceptible) = (0.286) × (1 − 0.525) = 0.286 × 0.475 = 0.136
- Pr(fatality is final outcome | QD-susceptible) = Pr(fatality | severe initial outcome) × Pr(severe initial outcome | QD-susceptible) + Pr(fatality|treatment failure) × Pr (treatment failure | QD-susceptible) = 0.37 × (1 − 0.286) + 0.286 × 0.525 = 0.4143
  - Pr(fatality | severe initial outcome and QD-susceptible) = 0.37
  - Pr(severe initial outcome | QD-susceptible)=1−0.286 = 0.714
  - Pr(QD treatment failure | QD-susceptible) = 0.286
  - Pr(fatality | QD treatment failure) = 0.525 (see Fig. A1).

Table A1 summarizes results for susceptible and resistant cases.

Table A1. Estimated probabilities of different adverse health outcomes from infections with food-borne QD-susceptible and QD-resistant VREFs

Bacterium	Final health outcome		
	Severe illness only	QD treatment failure	Fatality
QD-susceptible VREF	0.45	0.136	0.4143
QD-resistant VREF (SREF)	0	0.475 = 1 − 0.525	0.525

A.2. Severity of consequences: QALY losses due to excess mortality and morbidity

VREF patients in a recent study (Webb et al., 2001) incurred an average of 14.6 additional days of hospitalization compared to VSEF patients (34.2 days vs. 48.8 days). No analogous study for QDREF versus QDSEF patients is available, perhaps because of the small numbers of QDREF patients. We will assume that the additional number of days of treatment attributable to QD resistance or treatment failure is the same as the additional days attributable to vancomycin resistance, i.e., 14.6 days.

Extra days of treatment and illness can be converted to lost quality-adjusted life-years (QALYs). The HUI3 multi-attribute utility scale (Furlong et al., 2001) provides values from −1.371 to 1.00, with negative scores representing states considered to be worse than death. Other scoring systems provide values from 0.0 to 1.0. HUI3 requires rating patients in eight health attributes with scores ranging from 1 to 6 and converting the results to a single value via Multi-Attribute Utility Theory (Cox, 2001). For simplicity, we will use a conservative overall rating of 0.0 for VREF patients with QD resistance during their treatment. The average number of QALYs lost per case are then as follows:

- Severe (susceptible): 48.8/365=0.1337
- Treatment failure (susceptible or resistant): 63.4/365= 0.1737

Thus, each treatment failure (e.g., due to QD resistance) is expected to generate an additional 0.04 QALYs lost per nonfatal treatment failure. This is a conservative estimate, as it *assumes that no other effective therapies are applied* following QD failure.

The QALY's lost per fatality is estimated by first comparing the average age of a VREF patient to average life expectancy. A study of 262 VREF patients in the United States determined a mean age of 60 years, composed of 55% females and 45% males (Webb et al., 2001). The current life expectancy at age 60, based on insurance actuarial tables, is 79.47 for males and 83.52 for females (InfoChoice, 2002;

we do not calculate separate values for the US and Australia for purposes of this rough estimate). Therefore, the estimated average QALYs lost per attributable fatality is $0.55 \times (83.52 - 60) + 0.45 \times (79.47 - 60) = 21.70$ years. This number is conservative (risk-maximizing), in that it assumes that a seriously ill VREF patient would have the same life expectancy and QALYs as a member of the general population if QD therapy were effective.

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