Assessing Potential Human Health Hazards and Benefits from Subtherapeutic Antibiotics in the United States: Tetracyclines as a Case Study

Louis Anthony (Tony) Cox Jr.* and Douglas A. Popken

Many scientists, activists, regulators, and politicians have expressed urgent concern that using antibiotics in food animals selects for resistant strains of bacteria that harm human health and bring nearer a “postantibiotic era” of multidrug resistant “super-bugs.” Proposed political solutions, such as the Preservation of Antibiotics for Medical Treatment Act (PAMTA), would ban entire classes of subtherapeutic antibiotics (STAs) now used for disease prevention and growth promotion in food animals. The proposed bans are not driven by formal quantitative risk assessment (QRA), but by a perceived need for immediate action to prevent potential catastrophe. Similar fears led to STA phase-outs in Europe a decade ago. However, QRA and empirical data indicate that continued use of STAs in the United States has not harmed human health, and bans in Europe have not helped human health. The fears motivating PAMTA contrast with QRA estimates of vanishingly small risks. As a case study, examining specific tetracycline uses and resistance patterns suggests that there is no significant human health hazard from continued use of tetracycline in food animals. Simple hypothetical calculations suggest an unobservably small risk (between 0 and 1.75E-11 excess lifetime risk of a tetracycline-resistant infection), based on the long history of tetracycline use in the United States without resistance-related treatment failures. QRAs for other STA uses in food animals also find that human health risks are vanishingly small. Whether such QRA calculations will guide risk management policy for animal antibiotics in the United States remains to be seen.

KEY WORDS: Acne; animal antibiotics; antimicrobial risk assessment; MRSA; Preservation of Antibiotics for Medical Treatment Act (PAMTA); resistance risks; tetracycline

1. INTRODUCTION: STA REGULATION

This article discusses potential human health risks from continued use of subtherapeutic amounts of antibiotics to promote health and growth and prevent bacterial infections in food animals in the United States. Throughout, we use “subtherapeutic” to refer to nontreatment-related doses; these may have health benefits for animals, but are not prescribed as therapy for treating diseases. The first part of the article, comprising Sections 1–7, discusses risk management policy making with and without formal risk assessment. We contrast risk management based on an intuitively plausible narrative, suggesting that failing to stop animal antibiotic use now may imperil human health by promoting the spread of antibiotic-resistant “super-bugs,” with risk management based on a more formal risk assessment approach that suggests that human health risks from this easily
imagined scenario are probably quantitatively negligible. These styles pit a powerful intuitive and visceral emotional response to a terrifying scenario against the more reassuring results of highly cognitive and analytic data-driven calculations. Which will end up shaping U.S. policy remains to be determined. Sections 8–10 consider a specific, important example: hazard analysis of the continued use of tetracycline antibiotics. This is a very widely used class of antibiotics, and the one with the highest levels of resistance in multiple species of food-borne bacteria.

The current debate over subtherapeutic antibiotics (STAs) illustrates a crucial question for the future role of risk analysis in public policy: Does formal health risk analysis provide a trustworthy basis for making key risk management policy decisions? How well can risk analysis succeed in guiding risk management policy making, especially when intuition suggests easily imagined, vivid catastrophic consequences (e.g., accelerated deterioration of the efficacy of life-saving antibiotics in human medicine) from failure to act promptly (e.g., by banning continued use of STAs), but risk analysis indicates that the feared risks are actually trivial, and that recommended interventions are likely to do much more harm than good? We see management of human health risks from STAs as a test of whether formal risk analysis, or more intuitive political approaches, will guide public health decision making when the two seem (at first) to conflict.

The following Sections 2–7 frame the current debate over continued STA use in terms of alternative approaches to risk management—formal and analytic versus intuitive. They compare U.S. and European experiences, as illustrating risk analysis-driven and more intuitive, precautionary risk management policy making, respectively. Sections 8–10 focus on tetracyclines as an important class of antibiotics, identified by STA opponents as a priority for removal, and consider sources of data and empirical evidence for assessing potential threats to human health from their continued use. The purpose is to compare risks of continued tetracycline use, as viewed from the perspective of formal risk analysis (specifically, hazard identification based on methodical consideration of specific uses and treatment failure data) with the same risks as perceived from the perspective of a more holistic, intuitive assessment, based on a mental model for how continued use might harm human health. These views may drive quite different policy recommendations and priorities.

### 2. POTENTIAL HUMAN HEALTH RISKS AND BENEFITS FROM STA USE

Subtherapeutic concentrations of antibiotics have long been used in feed and water to prevent disease and to promote health and growth in food animals. Such uses have at least two possible effects on human health (e.g., Phillips, 2007). On the one hand, conventional wisdom holds that healthy animals make for healthy people. STAs improve animal health and reduce microbial loads in meats, thereby presumably reducing the potential for food-borne illnesses (Hurd et al., 2008; Arnau et al., 2007; Singer et al., 2007). STAs can promote growth, particularly in poultry and hogs, by improving nutrient absorption and by depressing the growth of organisms that compete for nutrients, thereby increasing feed efficiency (MacDonald and McBride, 2009). On the other hand, routine use of antibiotics in food animals selects for antibiotic-resistant strains of bacteria in the GI tracts of food animals (e.g., Inglis et al., 2005). If these resistant bacteria were to spread in the environment, or survive through the food chain, in sufficient concentrations to cause food poisoning when people eat raw or undercooked meats, and if the resulting illnesses were then treated with antibiotics to which the bacteria are resistant, then treatment might be less effective than if the infecting strains of bacteria were more susceptible to the prescribed antibiotics (Slaughter, 2008). This frightening scenario has great narrative plausibility; it stirs the imagination. Whether it could occur in reality depends on numerous prosaic details of food processing, food preparation, microbiology, and clinical practice, such as whether bacteria survive the trip from farm to fork; whether physicians screen for resistance before prescribing an antibiotic; whether prescribed doses are sufficient to kill even resistant bacteria; and whether hospitals serve raw or undercooked meat to severely immunocompromised patients in intensive care units.

Whether the human health benefits are greater or less than the human health harms from STA use has seldom been quantified. Rather, the possibility of harm is often pointed to as a sufficient reason to ban STAs, without further analysis or comparisons (ibid). Europe has accepted this view, and accordingly has phased out STAs; the United States has not done so in the decade since the EU bans, however. The rationales for these different risk management responses, and subsequent public health experiences in the United States and Europe, are discussed next.
3. EUROPEAN AND U.S. REACTIONS TO PRESSURES TO BAN STA USE

The usual medical consequence of reduced effectiveness of antibiotic therapy for food-borne illnesses is extra hours or days of diarrhea (e.g., FDA-CVM, 2001). In severely ill patients with compromised immune systems (such as AIDS, leukemia, or organ transplant patients), however, antibiotic-resistant zoonotic infections can be life-threatening. For decades, envisioning hypothetical scenarios in which animal antibiotic use increases the rate of antibiotic treatment failures in desperately ill human patients has spurred many activists, scientists, physicians, and some politicians to repeatedly call for bans on the use of STAs in food animals.

In response, starting in the late 1990s, the European Union phased out growth promoting STA use, invoking the precautionary principle as justification, despite the recommendations of scientific reviewers who pointed out that STA use has no apparent causal link to resistance rates in human infections in the real world (Pugh, 2002). The United States has not yet done so, largely because its regulators have refused to withdraw products that benefit animals (and, thereby, perhaps human health) when empirical data do not show that they harm human health.

For many regulators in the United States, initial narrative plausibility and activist outrage do not (as of this writing) provide adequate bases for regulation. They insist that regulatory action should reflect verifiable empirical data and risk assessment, showing that advocated interventions address real problems (supported by empirically valid cause-and-effect relations, rather than only by envisioned scenarios), and that they are likely to create real public health benefits (rather than no change, or unintended public health harm). But political pressure on Congress remains strong to eliminate STAs, without further empirical research or quantitative risk assessment. This pressure comes in part from concerned activist groups, such as Keep Antibiotics Working (KAW, 2009); in part from concerned scientists and physicians (UCS, 2009; Simmons, 2007); and in part from powerful politicians in Congress (Pew, 2009; Simmons, 2007).

The possibility of using political concern, rather than probable health consequences, as a basis for STA regulation has been strengthened by the 2003 release of FDA’s Guidance Document for Industry #152 (FDA-CVM, 2003). This document allows qualitative expressions of concern to be mapped to recommended levels of risk management priority, with no need to consider how or whether recommended interventions would change human or animal health risks. Mathematical analysis shows that this qualitative approach can ignore information that is logically necessary to correctly compare risks, leading to worse-than-random risk management decisions and resource allocations (Cox et al., 2005; Cox, 2008). Guidance Document #152 does not seek to evaluate the changes in human health that would be caused by withdrawing STAs, but instead provides a framework for documenting levels of concern (e.g., as “High,” “Medium,” or “Low,”) based on factors such as the judged “importance” level (e.g., “Very Important” or “Critically Important”) of classes of antibiotics for human medicine. Such concern-based risk management frameworks can support actions that exacerbate the problems they mean to remedy (Cox, 2007). In response to Guidance Document #152, several animal pharmaceutical companies have taken the initiative to supplement their review submissions with additional quantitative data or risk analyses.

4. EVIDENCE OF CAUSALITY: ATTRIBUTION ASSUMPTIONS VERSUS EMPIRICAL DATA

Pressure to phase out STAs in the United States is buttressed by a widespread and much-repeated belief—presented as fact in many peer-reviewed scientific journal articles, as well as in less formal sources—that STA use in food animals has been causally linked, via consumption of resistant bacteria transmitted via the food chain, to increased rates of real-world treatment failures and harm in humans (e.g., Mølbak, 2004; Slaughter, 2008). However, we believe that this ubiquitous impression is mistaken—that it is only a scientific urban legend. It is based largely on epidemiological studies that misinterpret regression coefficients or odds ratios in multivariate statistical risk models, between food consumption patterns and resistant illnesses, as evidence of causal relations (e.g., Angulo et al., 2004; Varma et al., 2006); such causal interpretations are in general not justified (Cox, 2005). To our knowledge, no case of a treatment failure in a human patient, caused by transmission of antibiotic-resistant bacteria through the food chain (“from farm to fork”), has ever been documented in the United States. Nor have decades of efforts by groups such as the Alliance for Prudent Use of Antibiotics, as well as many regulatory
scientists, microbiologists, and physicians, succeeded in showing that STA use has had any adverse impact on human health via food-borne transmission of resistant bacteria. Rather, it has become common to simply assume, and then to assert, that STA use harms human health. This is sometimes done by first estimating “attributable fractions” that assign some (perhaps subjectively estimated or hypothetical) proportion of human treatment failures to STAs (e.g., Barza and Travers, 2002) and then treating this assumption as if it were valid empirical data or evidence (e.g., Angulo et al., 2004). Regulators, activists, and politicians routinely refer to such assumptions, estimates, and attributions as “evidence” of a causal relationship between STA use and increased human health harm, but they are not. For the same methods can be used equally well (or badly) to create a positive statistical relation between any two positive random variables, even if they are completely unrelated (statistically independent), or are negatively related (Cox, 2005). Such force-fit “evidence” is not evidence at all.

5. A POLITICAL APPROACH TO RISK MANAGEMENT WITHOUT RISK ANALYSIS

The reasoning and rhetoric now being used to urge Congress to halt STAs use in the United States are well illustrated in the following congressional testimony (Slaughter, 2008):

We cannot in good conscience stand by while our life-saving antibiotics become obsolete. While overuse of antibiotics among humans is certainly a major cause for increasing resistance, there is evidence that the widespread nontherapeutic use of antibiotics in animal feed is another cause of heightened resistance. A National Academy of Sciences report states that, “a decrease in antimicrobial use in human medicine alone will have little effect on the current situation. Substantial efforts must be made to decrease inappropriate overuse in animals and agriculture as well.” … The nontherapeutic use of antibiotics in poultry skyrocketed from 2 million pounds in 1985 to 10.5 million pounds in the late 1990s. This kind of habitual, nontherapeutic use of antibiotics has been conclusively linked to a growing number of incidents of antimicrobial-resistant infections in humans, and may be contaminating ground water with resistant bacteria in rural areas. … During discussions involving the now-enacted Farm Bill, I supported language which would have provided the farm industry with sound, scientific information on production practices that could have helped them reduce their dependence on antibiotics and meet the growing consumer demand for meat produced without these drugs.

The ability to grow food animals with fewer antibiotics would have also given US exporters an advantage in the international marketplace. … Disappointingly, however, industry successfully lobbied to strip this language out of the Farm Bill. … I am also the sponsor of H.R. 962, the Preservation of Antibiotics for Medical Treatment Act (PAMTA). This bill requires three actions to accomplish the goal of reducing antibiotic resistance in humans. PAMTA would phase out the use of the seven classes of medically significant antibiotics that are currently approved for nontherapeutic use in animal agriculture. … [I] cannot stress the urgency of this problem enough. When we go to the grocery store to pick up dinner, we should be able to buy our food without worrying that eating it will expose our family to potentially deadly bacteria that will no longer respond to our medical treatments.

From the standpoint of sound risk analysis and risk management policy making, such impassioned statements are striking for several reasons. First, there is no apparent examination of whether discontinuing STA use will actually help human health, or harm it. There is no discussion of whether improved food safety from reduced bacterial loads in meats, or increased risks of antibiotic resistance among bacteria that survive, dominates the public health impacts of STA use. Instead, the statement moves directly from a problem statement (antibiotic resistance in human bacterial infections threatens human health) to a recommended solution (discontinue STA use in food animals), by way of an assumption (that eating meat will expose families to “potentially deadly bacteria that will no longer respond to our medical treatments”). There is no attempt to apply the usual intermediate risk analysis steps of quantifying the claimed risk and explicitly assessing, documenting, and comparing the probable consequences of risk management alternatives, such as continuing versus discontinuing prudent use of STAs to promote health. Yet, these omitted steps are the heart of rational risk analysis.

5.1. Quantitative Versus Qualitative Descriptions of Risks

Second, the above calls for urgent action do not quantify the hoped-for reduction in risk that their advocates presumably anticipate will result from the proposed interventions. The dreaded nature of the envisioned scenario (families around their dinner tables being exposed to untreatable, deadly bacteria) is vividly expressed, but the frequency and severity of resulting preventable adverse health consequences, if any, are not described. When this is done, the resulting numbers turn out to be vanishingly small,
robbing the dramatic narrative and urgent calls for prompt action of much of their visceral appeal. For example:

- For macrolides, Hurd and Malladi (2008) concluded that “the predicted risk of suboptimal human treatment of infection with C. coli from swine is only 1 in 82 million; with a 95% chance it could be as high as 1 in 49 million. Risks from C. jejuni in poultry or beef are even less.”
- For penicillin, Cox et al. (2009) calculated that “not more than 0.037 excess mortalities per year (under conservative assumptions) to 0.18 excess mortalities per year (under very conservative assumptions) might be prevented in the whole U.S. population if current use of penicillin drugs in food animals were discontinued, and if this successfully reduced the prevalence of antibiotic-resistant E. faecium infections among intensive care unit (ICU) patients.” They note that the true risk could well be zero.
- For streptogramins, banning virginiamycin has been estimated to prevent from 0 to less than 0.06 statistical mortalities per year in the entire U.S. population (Cox and Popken, 2004; see also FDA-CVM, 2004).

Such specific, small risk numbers may be less likely to incite congressional intervention than the broad qualitative assertion that “[w]e should be able to buy our food without worrying that eating it will expose our family to potentially deadly bacteria that will no longer respond to our medical treatments.” In fact, the “deadly” bacteria referred to, including commensals such as MRSA, Campylobacter, and E. faecium, are routinely found—and are harmless—in healthy people (and other birds and mammals) with normally functioning immune systems. They become life-threatening only under very unusual and rare circumstances, especially for patients with severely compromised immune systems, such as AIDS, leukemia, and transplant patients, typically in ICUs. Attributing the risks from such rare, dire, medical circumstances to consumption of meat at family meals is perhaps effective rhetoric, but it is poor microbiology. Such qualitative, concern-driven risk management, stripped of relevant risk numbers, data, alternatives, causation, and consequence estimates, may motivate political support for interventions, but it can also encourage different, less effective, risk management recommendations than would result from sound QRA (Cox, 2007).

5.2. Data-Driven Hazard Identification Versus Unverified Causal Assertions

A third aspect of the above statements on the rationale for phasing out STAs in the United States also differs sharply from the typical, more cautious, risk analysis presentation of verifiable facts, data, and models to support specific quantitative conclusions. This is their reliance on sweeping qualitative causal claims: specifically, that “[a] decrease in antimicrobial use in human medicine alone will have little effect on the current situation,” (which appears to be a misquote of the much weaker statement that “[c]learly, a decrease in the inappropriate use of antimicrobials in human medicine alone is not enough.” http://books.nap.edu/openbook.php?isbn=030908864X&page=207) and that “[t]he ability to grow food animals with fewer antibiotics would have also given US exporters an advantage in the international marketplace.” Hazard identification—the part of risk assessment that traditionally considers evidence for (and against) hypothesized risks and exposure-response relations, and the empirical bases for claimed adverse effects—shows that these claims are not well supported by data.

The assertion that banning STAs would create “an advantage in the international marketplace,” made without reference to any specific supporting data, contrasts strongly with the historical experiences of countries that have tried it. For example, Sweden banned STAs in 1986. “The Swedish experience shows that antibiotics are not necessary to produce healthy animals, provided their living conditions, rearing and foods are improved. This did come at a cost: thousands of pigs and chickens probably died as a direct result of the ban, despite the overall improvement in animal welfare. Swedish produce is more expensive, and so less competitive on the market, and the costs of the venture are expensive” (Hughes and Heritage, 2004, emphasis added). Norway and the United Kingdom had similar experiences. The problem was great enough in those countries that alternative, prescription antibiotics were introduced in response to significant enteric diseases in poultry (Van Immerseel et al., 2009).

The crucial, policy-relevant generalization that “a decrease in antimicrobial use in human medicine alone will have little effect on the current situation” is flatly contradicted by many quantitative studies over many years. For example, more than a decade ago, there were already “more than 20 studies on consistent associations, dose-effect
relationships, and concomitant variations, all supporting a causal relationship between [human patient] antimicrobial-drug use and MRSA” (Monnet and Frimodt-Moller, 2001). Gould (1999) noted that: “Early studies in various hospitals showed rapid reversal of major clinical problems of resistance to chloramphenicol, erythromycin and tetracycline in Staphylococcus aureus on withdrawal of these antibiotics from clinical use.” Moreover, “[in the community, outbreaks of erythromycin-resistant Group A streptococci and penicillin-resistant pneumococci have been controlled by major reductions in prescribing of erythromycin and penicillin.” They conclude that “there is little doubt that careful antibiotic prescribing can curtail the emergence and reduce the prevalence of resistance” in these and other bacteria.

Similarly, Aldeyab et al. (2008) studied in detail the variance in monthly incidence of Methicillin-resistant Staphylococcus aureus (MRSA) over a 5-year period in one hospital. They found that “temporal variations in MRSA incidence followed temporal variations in the [human] use of fluoroquinolones, third-generation cephalosporins, macrolides and amoxicillin/clavulanic acid (coefficients = 0.005, 0.03, 0.002 and 0.003, respectively, with various time lags).” Over three-quarters of the monthly variance in MRSA was explained by a model that included only these human antibiotic usage variables (which increase MRSA prevalence) and infection controls (which reduce it). Fig. 1 shows results from a similar 2004 study. Again, decreasing antimicrobial use in human medicine alone dramatically reduced subsequent MRSA rates. A time series model of MRSA changes over time, with only human antibiotic use as exogenous explanatory variables, accounts for over 90% of the observed variance in MRSA rates. In short, not only is it untrue that “a decrease in antimicrobial use in human medicine alone will have little effect on the current situation” (Slaughter, 2008), but in many studies, over many years, it is almost the only thing that does have an effect.

Other time series analyses have revealed that, instead of MRSA first increasing in the community (e.g., from families eating contaminated meat) and then infiltrating hospitals as sick patients enter, the flow is in the opposite direction: “[W]e demonstrated that variations in MRSA prevalence in the hospital are quickly followed by similar variations in MRSA prevalence in the surrounding community. These results suggest that the reason for the increase in MRSA prevalence in the community was a hospital MRSA outbreak” (MacKenzie et al., 2007).

Traditional risk analysis typically avoids making sweeping generalizations about causal relations (such as that “a decrease in antimicrobial use in human medicine alone will have little effect”), in favor of displaying relevant data supporting more specific, quantitative, causal claims. This more cautious, empirically driven, approach tries to reduce the likelihood that decision makers will adopt wholly false beliefs about what works, and hence will urge ineffective or harmful policies based on such mistaken beliefs. Hence, risk analysts typically put hazard identification early in a risk assessment, insisting that empirical evidence of causal relations be documented and scrutinized before undertaking further quantification of exposure-risk relations. In the present example of resistance risks, a well-conducted hazard identification would consider time series studies and data showing that changes in human antibiotic use precede, and explain, almost all of the subsequent changes in antibiotic resistance in isolates from humans (MacKenzie et al., 2007). It would examine time series data showing that changes in infections in humans tend to precede, rather than to follow, corresponding changes in Campylobacter prevalence in chicken flocks (Christensen et al., 2001). It would consider evidence that resistant bacteria are transmitted from humans to food animals, and from environmental sources (e.g., flies, soil, water) to both, and would consider the extent to which these flows might explain instances of similar or identical bacteria in different species (e.g., Herron-Olson et al., 2007). Such relevant empirical data would be evaluated, critically discussed, and synthesized in the hazard identification section of a typical risk assessment before assuming (or asserting) that changes in animal consumption of STAs drive changes in resistance to infections in hospitalized patients.
Policies based on inadequate understanding of causal relations can produce the opposite of their intended effects, e.g., by inducing shifts in antibiotic use that unintentionally increase costs and harm to human health (Beilby et al., 2002), or that increase animal use of therapeutic antibiotics that threaten human health more than the STAs that they replace (Casewell et al., 2003). If decisionmakers are mistakenly told that reducing STA use will significantly reduce resistant infections in human patients, but that reducing human medical antibiotic use alone would make little difference, then interventions based on such assumptions may not achieve their intended public health goals. Risk management policies based on false causal premises—no matter how well intended, or how sincerely and passionately urged—cannot be expected to cause desired changes. Risk analysis, unlike many other political and precautionary approaches, therefore focuses on understanding—and, when possible, even quantifying—the probable causal effects of different interventions on outcomes of concern, prior to recommending risk management interventions. Correct, usefully detailed, causal understanding and quantitative modeling of effects and tradeoffs may be essential for effective intervention in systems as complex and difficult to control as antibiotic resistance in human infections. Otherwise, well-intended, common-sense interventions may backfire, producing the opposite of their intended effects (e.g., Beilby et al., 2002).

6. EMPIRICAL EVIDENCE FROM THE UNITED STATES AND EUROPE: DO STAs HARM OR HELP HUMAN HEALTH?

Empirically, how has STA use affected human health in the United States? Conversely, how has withdrawal of STAs affected human health in Europe? Although unambiguous causal interpretation and explanation of historical trends is admittedly challenging, and any such interpretation of resistance trends is at present only hypothetical, the above testimony (Slaughter, 2008) emphasizes that nontherapeutic use of antibiotics in poultry had “skyrocketed” in the United States by the late 1990s—a history that should help to reveal the human health consequences (if any) of rapidly increasing STA use. Continued use of STAs in the United States was followed by improvements in microbial safety and zoonosis-related human health. For example, microbial loads of campylobacter in poultry dropped to perhaps 10% of their previous levels by 1995, while human campylobacteriosis health risks decreased significantly (Stern and Robach, 2003). Use of animal antibiotics in the United States coincided with reduced risks of many other food-borne illnesses, too: “In comparison with 1996–1998, relative rates of Yersinia decreased 49% (CI = 36%–59%), Listeria decreased 42% (CI = 28%–54%), Shigella decreased 36% (CI = 9%–55%), Campylobacter decreased 31% (CI = 25%–36%), STEC O157 decreased 25% (CI = 9%–38%), and Salmonella decreased 8% (CI = 1%–14%) in 2007” (CDC, 2008). These declines in food-borne illness rates were largely accomplished by 2004, and have generally persisted since, while most antibiotic resistance rates in zoonotic bacteria have remained stable or declined (Cox and Ricci, 2008; NARMS, 2009).

Even as the United States was enjoying falling levels of campylobacteriosis and other food-borne illnesses, multiple European countries that had ceased using STAs experienced significant increases in human illnesses due to food poisoning, including campylobacteriosis (Vierikko et al., 2004) and other zoonotic bacteria. Increased human illnesses were accompanied by greater human use of antibiotics and, ironically, by jumps of up to several hundred percent in some antibiotic resistance rates in human patients (Hayes and Jensen, 2003). Most of these changes were complete by about 2004, and extensive recent interventions to control Salmonella and Campylobacter have achieved some successes (Cox, 2007). Nonetheless, a decade after the bans, Denmark, a long-time leader in implementing and advocating bans on STAs, and in collecting data to monitor the results, reported that mean hospital consumption of antibiotics had increased by 63% between 1997 and 2007, leading some reviewers to note that: “Overall, Denmark’s position as a country characterised by rational use of antibiotics and a low occurrence of resistance is under pressure, and initiatives to counter such tendency are needed” (EPI-NEWS, 2008).

It is notoriously difficult to draw valid causal inferences from such aggregate (“ecological”) longitudinal observational data alone, and the logical fallacy of inferring causation from temporal sequence (post hoc, ergo propter hoc) must be avoided. Valid causal inference requires more detailed causal analyses and models, such as the time series analyses discussed above (see Fig. 1). However, it is clear that any hopes that withdrawing STAs in Europe would cause substantial reductions in serious antibiotic
resistance problems in human patients have not been well supported by historical experience.

7. PREVIOUS HUMAN HEALTH RISK-BENEFIT COMPARISONS FOR STAs

Europe’s acceptance of the precautionary principle encourages policymakers to implement well-intended, popular policy interventions, even if their true human health (and other) consequences cannot yet be predicted. In the United States, by contrast, regulators have been less willing to experiment with discontinuing STAs than in Europe. Predictions of how withdrawing STAs would probably affect human health in the United States must therefore be based on risk assessment models, rather than on historical experience.

Relatively few studies have explicitly compared the human health benefits to the potential human health risks of continued STA use in the United States. Studies that have made this comparison have not generally favored discontinuing use. For example, for virginiamycin, potential human health benefits from illnesses prevented have been estimated to be more than 10,000 times greater than potential human health risks from increased resistance (which are estimated to be less than 1 excess treatment failure-related mortality per decade in the U.S. population) (Cox and Popken, 2004). For macrolides, human health benefits from continued use (due to human illnesses prevented by safer food) have been estimated to exceed the human health costs, due to human illnesses prolonged by resistance, by a ratio of more than 1,000:1 (Cox and Popken, 2006). For other STAs, direct comparisons of human health benefits and costs are not yet available.

8. ASSESSMENT OF HUMAN HEALTH HAZARDS FROM TETRACYCLINE RESISTANCE

It is easy to extol the virtues of proper hazard identification as a prelude to risk assessment and risk management policy making, but useful hazard identification can be challenging when the specific exposures, harms, and pathways of interest are unknown or are very uncertain. For example, it has been hypothesized that using tetracyclines in food animals might help to select for bacteria, such as MRSA, \textit{E. coli}, or multidrug resistant (MDR) strains of \textit{Salmonella} that also resist other antibiotics (e.g., Akwar \textit{et al.}, 2008) and this co-selection might create risks larger than those from resistance to tetracyclines \textit{per se}. Past risk analyses of animal-use antibiotics have generally focused on ones with human-use counterparts used to treat illness caused by food-borne pathogens such as \textit{E. coli}, \textit{Campylobacter}, \textit{Salmonella}, and \textit{Enterococcus} (FDA-CVM, 2001; Cox and Popken, 2002, 2004; FDA-CVM, 2004; Alban \textit{et al.}, 2008; Hurd \textit{et al.}, 2008; Cox \textit{et al.}, 2009). By contrast, tetracyclines, while heavily used in both animals and humans, are not typically used to treat food-borne diseases. Therefore, hazard identification must consider how they are used, as well as evidence about co-selection hazards (i.e., the potential for bacteria that are resistant to one drug to be selected by exposure to another). A literature search identified MRSA and multidrug resistant (MDR) \textit{Salmonella} as possible co-selection concerns; they are examined next.

8.1. Assessment of Potential Hazard from Co-Selection of MRSA by Tetracycline STAs

Recent research in Denmark (Lewis \textit{et al.}, 2008) has identified a specific strain of MRSA, CC 398 (also called ST 398), that is associated with pigs, but that is increasingly being found in humans living or working on a farm with animals. MRSA is usually a harmless commensal; thus, the finding of the same bacteria in humans and pigs does not by itself indicate a health hazard. (Indeed, as noted by Morgan (2008), one might equally well hypothesize that humans are causing the spread of MRSA in pigs as the reverse; in neither case does carriage \textit{per se} imply infection or health harm.) However, the emergence and spread of community-acquired MRSA infections is a growing concern in several countries, including the United States.

In the United States, Smith \textit{et al.} (2008a) reported that 45% of farm workers and 70% of swine sampled on seven farms that were part of one closed system in east Iowa and west Illinois tested positive for MRSA. (Subsequent sampling (Smith, 2008b) brought the overall average down to 49% of swine, and confirmed the strain as ST398.) Another sampled establishment, in contrast, had no MRSA in pigs or workers. All MRSA samples were resistant to penicillin, oxacillin, and tetracycline. In a recent interview (Schneider, 2008), Dr. Smith suggested that animal use of tetracyclines was the “cause of the spread of [human] MRSA.” However, in a subsequent peer-reviewed publication (Smith \textit{et al.}, 2009), the authors carefully noted that “both production
systems that we sampled employ similar protocols for prophylactic and therapeutic use of antimicrobial agents, including tetracycline. Therefore, our data do not allow us to speculate on the relationship between antimicrobial use and MRSA carriage.” No MRSA types commonly found in human infections in North America (USA100, USA300, USA400) were reported. Politicians (Slaughter, 2008) and activists (KAW, 2008) have implicated animal antibiotic use in general as a cause of spreading MRSA, and have advocated curtailing all “inappropriate” (nontherapeutic) use of antibiotics in agriculture.

However, to go from the unsurprising observation that some humans that work around pigs carry the same strain of MRSA as pigs to the inference that animal uses of antibiotics [including tetracyclines] cause the spread of MRSA in human patients requires a leap across many unestablished causal links. For example, there is no evidence that tetracycline use in animals increases the spread or prevalence of animal MRSA, nor that MRSA in farm animals is conveyed to consumers on retail meats, nor that MRSA conveyed via meats could cause infections in consumers. Recent studies in the United States showed MRSA rates of 0% (Chan et al., 2008), 3% (Vedder, 2008), and 5% (Pu et al., 2009) in retail meat. DNA strain testing was only performed in the latter study, which found that none of the isolates was of type ST398. Therefore, no ST 398 strains have yet been found on retail meats in the United States.

A Dutch study of retail meats (van Loo et al., 2007) found 2 MRSA strains in 79 samples (2.4%), one of which was ST398, but that was present in “very low amounts” “not likely to cause disease.” Further, there have been no reports of MRSA ST398 among humans, other than farm workers, in the United States. Most strains are USA100 (health-acquired), or USA300 (community-acquired) (Klevens, 2007). The scenario in which MRSA ST 398 infects consumers via the food chain lacks empirical support.

Tetracycline resistance observed in MRSA does not, by itself, pose a health risk. Doxycycline is FDA-approved for the treatment of S. aureus skin infections, but not specifically for those caused by MRSA (CDC, 2006). Although international bodies such as WHO have sometimes classified tetracyclines as “Critically Important Antimicrobials,” on the grounds that they are “a limited therapy for infections due to MDR [multidrug resistant] S. aureus,” this appears to reflect a failure to distinguish appropriately between a relatively new drug, tigecycline, and older tetracycline drugs. In reality: “The only tetracycline in the WHO critically important list is a glycylcycline (tigecycline), the other class members are categorized as highly important. Due its resistance mechanisms, tigecycline is regarded as representing a different generation to other tetracyclines” (FAO/WHO/OIE, 2008, p. 31). Tigecycline, which was approved by the FDA in 2005 specifically to treat MRSA, is not used in food animals and it does not have the same resistance mechanisms or profile as tetracycline. Thus, it would be a mistake (a logical fallacy of composition) to classify tetracycline per se, or tetracycline drugs used as STAs, as “critically important” for human medicine, based on tigecycline.

Would banning STAs reduce the risk or speed of MRSA emergence? European experience suggests not. Concerns about the spread of MRSA from food animals to humans began in Europe, with the identification of pigs as a reservoir for human clonal complex (CC) 398 MRSA, in the Netherlands, France, Denmark, and later, Canada (Lewis et al., 2008). MRSA has developed and spread in these countries, undeterred by the fact that most growth promotion STAs (including tetracyclines and penicillins) have been banned there for many years. The observed easy spread of CC 398 MRSA among pigs and veterinarians (and other humans) in Europe (Wulf et al., 2008) suggests that the growth promotion STA bans do not prevent or noticeably inhibit this source of community-acquired MRSA. Tetracycline resistance (along with ciprofloxacin, erythromycin, and mupirocin resistance) is also commonly present in human strain USA300, which originated in urban settings in the early 2000s (Russell, 2008). This strain did not spread because of tetracycline exposures in agricultural settings, but because of human use. Moreover, as already noted in Fig. 1 and many other studies, MRSA in human patients overwhelmingly follows human use of antibiotics, especially quinolones (e.g., Aldeyab et al., 2008; Bosso and Mauldin, 2006; Tacconelli et al., 2008; Weber et al., 2003). Thus, we conclude that there is no evidence that STA use, including tetracycline use, contributes to the emergence and spread of either community-acquired or hospital-acquired MRSA infections in human patients. Although the hypothesis that STA use contributes to MRSA risk in human patients is perhaps intuitively plausible a priori, data do not support an inference that banning STAs would produce (or, in Europe, has produced) any detectable reduction in MRSA risks. But data do clearly indicate...
that reducing use of quinolones and third-generation cephalosporins in human medicine reduces MRSA risks.

8.2. Assessment of Potential Hazard from Co-Selection of MDR Salmonella by Tetracycline

The Salmonella species of most concern in the transmission of disease from animals to humans are Salmonella enteritidis and Salmonella typhimurium (WHO, 2005). These species cause gastroenteritis in humans, a condition that is often uncomplicated and does not require treatment, but may cause severe illness or even death in the young, elderly, or immunocompromised. For those needing treatment, fluoroquinolones are the drug of choice for adults, while third-generation cephalosporins are most often used for children or those who cannot tolerate fluoroquinolones. To a lesser extent, chloramphenicol, ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole are sometimes used (WHO, 2005); therefore, tetracyclines are not used in treating Salmonella.

Recent years have seen the development of various strains of multidrug resistant (MDR) Salmonella that are resistant to a variety of antimicrobials, including fluoroquinolones and cephalosporins. In this section, we examine the extent to which animal use of tetracycline causes or encourages the development of MDR Salmonella, particularly in swine, where tetracycline use is thought to be the most intense. For example, “the increasing significance of swine as reservoirs of emerging MDR serovars” has been identified as a recent public health concern (e.g., Patchanee et al., 2008). Common multidrug resistance patterns seen in swine include amoxicillin/clavulanic acid-ampicillin-chloramphenicol-piperacillin-tetracycline (Gebreyes et al., 2004); streptomycin, sulfamethoxazole, and tetracycline; and ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline [ACSSuT] (Gebreyes et al., 2006). The latter combination is typical of Salmonella serotype Typhimurium DT104, a species of worldwide concern. Of particular concern is the recent development of a penta-resistant form of Salmonella, serotype Newport MDR-AmpC, that is resistant to all of the ACSSuT antimicrobials as well as amoxicillin-clavulanic acid, cephalothin, cefoxitin, and cefotiofur, and exhibits decreased susceptibility to ceftriaxon. Note this includes second- and third-generation cephalosporins, the latter a Salmonella first-line treatment.

There is evidence that animal use of tetracyclines does not drive the development of MDR Salmonella, specifically including cephalosporin-resistant varieties. First, cephalosporin-resistant varieties of MDR Salmonella did not appear in the United States until the late 1990s, despite extensive use of tetracyclines in animal production in the United States since the 1950s, suggesting that this extensive use did not by itself select for cephalosporin cross-resistance. For example, Berge et al. (2004) examined samples of Salmonella enterica subspecies enterica serovar Newport from humans and animals taken in two time periods: 1988–1995 and 1999–2001. PFGE analysis showed that, while the genetic makeup of these two groups were similar, only the more recent samples were resistant to cephalosporins. A nationwide surveillance study of Ceftriaxone-resistant Salmonella infections in humans in the United States was undertaken by Dunne et al. (2000). The prevalence of ceftriaxone-resistant Salmonella was 0.1% (1 of 1,326) in 1996, 0.4% (5 of 1,301) in 1997, and 0.5% (7 of 1,466) in 1998. A study of multidrug-resistant (MDR) Salmonella Typhimurium in humans, retail meat, and food animals from Yucatan, Mexico was performed by Zaidi et al. (2007). MDR Salmonella typhimurium containing the blacMY-2 gene (confering cephalosporin resistance) rose from 0% (0/27) during 2000 and 2001 to 75% (63/84) in 2004 and 2005. It is apparent that widespread dissemination of cephalosporin-resistant Salmonella in North America is relatively recent. While this does not necessarily mean that tetracyclines play no role in the development of cephalosporin-resistant Salmonella, clearly other factors must be at work.

Secondly, Cephalosporin-resistant Salmonella actually appear to be relatively rare among swine. A study by Weigel and Isaacsen (2004) analyzed 207 Salmonella isolates taken from swine and environmental sources on 11 swine farms in Illinois. Ten of the 11 farms used tetracycline as a feed additive, but at varying rates. Resistance was tested to cephalosporin drugs, including cephalothin (1st generation), cefoxitin (2nd generation), cefotiofur (3rd generation), and ceftriaxone (3rd generation). Resistance was detected only for the first-generation cephalosporin, cephaparin, which had a total of 6 positive samples from two of the 11 farms with a total resistance prevalence rate of 6.8%. This study also showed only a weak association between antibiotic usage levels and prevalence of

Assessing Potential Human Health Hazards and Benefits from Subtherapeutic Antibiotics

441
Salmonella resistant to the same antibiotic. Gray et al. (2004) performed a large study of 5,709 Salmonella enterica isolates from a variety of animal species in the United States. A total of 112 isolates were resistant to ceftriofur and ceftriaxone and also possessed the bla_CMY gene. Ten of these were from the 1,580 swine isolates (0.6% resistance rate). Much higher resistance rates were found in isolates from other animals, as follows: horses (9.5%), cats (8.3%), turkeys (4.7%), dogs (4%), cattle (1.9%), and chickens (1%). Similarly, a large nationwide study by Varma et al. (2006) of Salmonella serotype Newport-MDR AmpC (which is cephalosporin-resistant) in humans found strong associations with previous use of antibiotics, and consumption of raw ground beef or runny eggs. They concluded that the infections are likely acquired through food with bovine or perhaps poultry sources.

We also examined evidence regarding whether tetracycline use may be responsible for the earlier seen forms of MDR Salmonella, dangerous in themselves, but that could also theoretically provide a stepping stone to the cephalosporin-resistant varieties discussed above. To examine this potential hazard empirically, Gebreyes et al. (2006, 2008) and colleagues (Thakur et al., 2007) compared antimicrobial resistance rates in 60 conventional and antimicrobial-free (ABF) swine production systems in three states. They found that Salmonella prevalence was significantly higher (by a factor of almost four-fold, 15.2% vs. 4.2%) among the antimicrobial-free systems than in the conventional systems. A significant proportion of the isolates from antimicrobial-free herds were resistant to a variety of antimicrobial agents. A multidrug resistance pattern with resistance to streptomycin, sulfamethoxazole, and tetracycline was commonly observed, but there was no significant difference in the proportion of isolates with this pattern between the conventional (19.5%) and the antimicrobial-free (18%) systems. The ACSSuT multiresistance pattern was also common in the antimicrobial-free herds. The authors interpret these data as “suggesting selective pressure other than antimicrobial use, could be important risk factors for the persistence of MDR Salmonella strains in the swine production environment” (Gebreyes, 2008).

Other researchers have examined genetic evidence and arrived at similar conclusions, that “antimicrobial selection pressure does not consistently explain the increased prevalence of epidemic MDR stains of S. enterica, and restricting antimicrobial use often fails to control the dissemination of epidemic MDR strains, suggesting that there may be other biological traits or genetic factors that increase bacterial virulence or fitness or at least compensate for a fitness cost mostly accompanied by antimicrobial resistance” (Kang et al., 2006). While these selective pressures are not fully understood, possible explanations are being investigated. Karatzas et al. (2008) showed that disinfectants commonly used on swine farms select for MDR Salmonella. Ricci and Piddock (2009) showed that Ciprofloxacin can select for genes partially responsible for MDR Salmonella.

In summary, we conclude that currently available data do not support the hypothesis that discontinuing use of tetracyclines in food animals would reduce risk of either MRSA infections or MDR Salmonella infections in human patients. That Salmonella prevalence is reduced approximately four-fold in swine reared with antibiotics in the United States, as compared to ABF swine (Gebreyes, 2008), also suggests potential benefits from continued use. Since we find no evidence of increased treatment failures in human patients due to co-selection of MRSA or MDR Salmonella from tetracycline use in food animals, as an alternative hypothesis, we turn next to potential hazards caused directly by tetracycline resistance in human medicine.

8.3. Assessing Potential Hazards from Tetracycline Resistance in Human Medicine

Tetracyclines have been used in human medicine to treat respiratory tract infections such as pneumonia; infections of skin, genital, and urinary systems; and infections that cause stomach ulcers (Helicobacter pylori). Doxycycline is the first-line treatment for Rickettsia diseases (spotted fever, typhus, and scrub typhus), including Rocky Mountain spotted fever in the United States; chloramphenicol is a second-line treatment (www.merck.com/mmpe/sec14/ch177/ch177a.html). Doxycycline is an alternative treatment for Lyme disease and, along with ciprofloxacin, is recommended by the CDC as a prophylaxis against inhalation-derived anthrax infections (Bell et al., 2002). FDA’s Guidance 152 document (FDA, 2003) lists tetracyclines as “Highly Important” in human medicine (on a scale of “Critically Important,” “Highly Important,” and “Important”); this designation includes the specific drugs tetracycline, chlorotetraycline, demeclocycline, doxycycline, and minocycline. The rationale checked in the justification column is “Sole/limited therapy...
or essential therapy for serious diseases,” and the comments column (examples) specifies “Rickettsial disease: Anthrax therapy/prophylaxis.” However, in reality, many other antibiotics, can be used to treat anthrax infections (AHFS, 2008; Zeichner, 1998; Bell et al., 2002). Tetracycline is sometimes mentioned as a treatment option for “traveler’s diarrhea,” i.e., E. coli enteritis (Klein and Cunha, 1995; Sack et al., 1978), but most such cases are self-limiting and resolve within 1–3 days without medication (NIH, 2008).

In addition to killing or inhibiting growth of bacteria, tetracyclines are effective for prophylaxis and treatment of malaria due to Plasmodium falciparum, including that due to mefloquine-resistant P. falciparum (Roberts, 2003). They also have useful anti-inflammation, immunosuppression, dental, and wound-healing effects that are useful for treating noninfectious conditions, such as rosacea, and that enhance their effectiveness in treating acne. Tetracyclines are one of the cheapest classes of antibiotics available today, making them attractive for use in developing countries with limited health care budgets.

8.3.1. Tetracycline Prescription Rates in Europe and the United States

In the United States, tetracycline drugs are prescribed for outpatient use at a higher rate than any other antibacterial, except for penicillins, at 4.63 defined daily doses per 1,000 population per day (DDDs) in 2004 (Goossens et al., 2007). This represented 18.6% of total DDDs for all outpatient antibiotics in the United States. In Europe, the average tetracycline outpatient prescription rate for 2004 is 2.37 DDDs, representing 12.42% of all antibiotics (ibid). A significant portion of this tetracycline use goes to treating acne and rosacea, as these often require prolonged treatment periods. Acne treatment guidelines indicate taking oral antibiotics for between 3 and 6 months (Helms et al., 2006). Using prescription survey data from Stern (2000), and assuming that each prescription provides an average of 90 days of tetracycline use, yields an estimate of 157,680,000 doses prescribed annually. Based on the U.S. population at the time of the survey, this equates to 1.58 DDDs for tetracycline use in treating acne, roughly one-third of all human tetracycline use in the United States.

8.3.2. Survey of Tetracycline Resistance Hazards for Human Medical Uses of Tetracyclines

Table I summarizes current human uses of tetracyclines worldwide, as both primary and alternative antibiotic selections (Roberts, 2003). It notes the U.S. incidence of each disease or condition being treated, as well as any resistance to tetracyclines by the underlying organism. It is striking that most of these conditions are not relevant as potential hazards (i.e., sources of human treatment failure risk) from animal tetracycline use in the United States.

This is because the underlying conditions are rare or nonexistent in the United States; or because tetracycline resistance remains rare or nonexistent; or because the condition is noninfectious (e.g., rosacea). It is unlikely that continued tetracycline use would suddenly increase the tetracycline resistance rates for these or other organisms in the United States, as tetracyclines have already been extensively used for decades. Table I lists specific reasons for excluding various conditions from further consideration. Estimated average annual cases, when originally provided as rates, are computed with an assumed U.S. population of 305M (76% of which is adult); when cases are originally provided only in the form of ranges, the midpoint of each range is assumed to be the average. A few rows indicate conditions for which tetracycline resistance cannot easily be classified as a negligible hazard in human medicine. These are analyzed further below.

Table I identifies only three organisms/conditions that could potentially create a nonzero risk of tetracycline resistance-related treatment failures at present in the United States. Among 28 identified organisms/conditions for which tetracycline is a treatment option, only the following three were identified as posing potential resistance hazards to effective therapy:

- **Periodontal disease** (gingivitis) a common condition for which tetracyclines are sometimes used as part of treatment, and for which resistance is both observable before treatment and inducible during treatment;
- **Acne vulgaris** (acne), which is very common, and for which tetracycline treatments induce significant resistance in vivo in the causative agent (P. acnes), as well as in the oral and fecal flora of patients and their family members;
- Possibly, **Mycobacterium fortuitum**, which is relatively rare in the United States, but in
<table>
<thead>
<tr>
<th>Organism/Condition</th>
<th>Common Name</th>
<th>U.S. Cases per Year</th>
<th>Treatments</th>
<th>Resistance to Tetracycline</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Plague</td>
<td>1 to 40 cases (avg = 13 cases) by western states, 1971–1995. <a href="http://www.cdc.gov/ncidod/dvbid/plague/facts.htm">http://www.cdc.gov/ncidod/dvbid/plague/facts.htm</a></td>
<td>Streptomycin is the antibiotic of choice. Gentamicin is used if streptomycin is not available. Tetracyclines and chloramphenicol are also effective. <a href="http://www.cdc.gov/ncidod/dvbid/plague/qa.htm">www.cdc.gov/ncidod/dvbid/plague/qa.htm</a></td>
<td>Extremely rare: 2 documented cases worldwide, none in the United States. <a href="http://aac.asm.org/cgi/content/full/50/10/3233#R28">http://aac.asm.org/cgi/content/full/50/10/3233#R28</a> none</td>
</tr>
<tr>
<td><em>Bartonella henselae</em></td>
<td>Cat-scratch disease</td>
<td>1 per 10,000 persons. <a href="http://www.emedicine.com/MED/topic212.htm">http://www.emedicine.com/MED/topic212.htm</a> (avg = 30,500)</td>
<td>CSD is typically a benign, self-limited illness lasting 6–12 weeks in the absence of antibiotic therapy (90%). Erythromycin and rifampicin are the antibiotics of choice in humans.</td>
<td>Susceptible. <a href="http://aac.asm.org/cgi/content/full/48/6/1921">http://aac.asm.org/cgi/content/full/48/6/1921</a></td>
</tr>
<tr>
<td><em>Rickettsia</em> species</td>
<td>Spotted fever (Rocky Mountain Spotted Fever)</td>
<td>250–1,200 cases of reported annually (assume avg = 725). <a href="http://www.cdc.gov/ticks/diseases/rocky_mountain_spotted_fever/statistics.html">www.cdc.gov/ticks/diseases/rocky_mountain_spotted_fever/statistics.html</a></td>
<td>Doxycycline. <a href="http://cmr.asm.org/cgi/content/full/18/4/719">http://cmr.asm.org/cgi/content/full/18/4/719</a></td>
<td>None observed to date (Roberts, 2003); see also Lorian (2005, p. 275)</td>
</tr>
<tr>
<td>Organism/Condition</td>
<td>Common Name</td>
<td>U.S. Cases per Year</td>
<td>Treatments</td>
<td>Resistance to Tetracycline</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>Atypical pneumonia</td>
<td>2 million cases and 100,000 pneumonia-related hospitalizations occur in the United States. <a href="http://www.cdc.gov/ncidod/dbmd/diseaseinfo/mycoplasmapneumonia_t.htm">http://www.cdc.gov/ncidod/dbmd/diseaseinfo/mycoplasmapneumonia_t.htm</a></td>
<td>Several antimicrobials are effective in reducing the length of illness due to mycoplasmal pneumonia, including erythromycin, azithromycin, clarithromycin, doxycycline, and quinolones.</td>
<td>To date, no clinical isolates resistant to tetracyclines have been described in the literature, but some have been selected in vitro. <a href="http://www.ingentaconnect.com/content/ben/cdtid/2005/00000005/00000003/art00006">http://www.ingentaconnect.com/content/ben/cdtid/2005/00000005/00000003/art00006</a>.</td>
</tr>
<tr>
<td>Mefloquine-resistant</td>
<td>A virulent type of malaria</td>
<td>None (at temperatures below 68°F, Plasmodium falciparum cannot complete its growth cycle in Anopheles mosquito, so cannot be transmitted). <a href="http://www.cdc.gov/Malaria/distribution_epi/distribution.htm">www.cdc.gov/Malaria/distribution_epi/distribution.htm</a> (assume avg ~0)</td>
<td>Mefloquine, quinine in combination with doxycycline, or Fansidar®. <a href="http://www.tulane.edu/~wiser/protozoology/notes/malaria.html">http://www.tulane.edu/~wiser/protozoology/notes/malaria.html</a></td>
<td>Susceptible. <a href="http://www.springerlink.com/content/90v379gry12mhl/,http://www.ajtmh.org/cgi/content/abstract/47/1/108">http://www.springerlink.com/content/90v379gry12mhl/,http://www.ajtmh.org/cgi/content/abstract/47/1/108</a></td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>Primary treatment alternative prophylaxis</td>
<td>Balantidiasis is found worldwide and has an overall estimated prevalence of 1% but is rare in the United States. Most cases of balantidiasis in immunocompetent individuals are asymptomatic. <a href="http://www.emedicine.com/MED/topic203.htm">www.emedicine.com/MED/topic203.htm</a> (assume avg ~0)</td>
<td>Tetracycline is the treatment of choice, with metronidazole being the primary alternative. Iodoquinol, puromycin, and nitazoxanide are also effective against balantidiasis. <a href="http://www.emedicine.com/MED/topic203.htm">www.emedicine.com/MED/topic203.htm</a></td>
<td>No tetracycline-resistant protozoans have yet been described (Roberts, 2003)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Organism/Condition</th>
<th>Common Name</th>
<th>U.S. Cases per Year</th>
<th>Treatments</th>
<th>Resistance to Tetracycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodontal disease</td>
<td>Gingivitis</td>
<td>44% to 57% of adults have moderate periodontitis, and about 7% to 15% have advanced periodontitis (Beck and Offenbacher, 2003) (assume avg ∼ 27M)</td>
<td>Mechanical procedures, oral rinses, and sometime antibiotics including tetracyclines (American Academy of Periodontology, 2001)</td>
<td>Villidieu et al. (2003) found 11% of oral microbial flora in healthy adults contains tetracycline resistance genes. Olsvik and Tenover (1993) found up to 75% of bacteria in subgingival flora may contain tetracycline resistance genes after long-term treatment</td>
</tr>
<tr>
<td>Acne vulgaris (P. acnes)</td>
<td>Acne</td>
<td>5.1 million antibiotic prescription for acne annually between 1996 and 1998 (Stern, 2000)</td>
<td>Combination treatments including tretinoin, benzoyl peroxide, topical antibiotics (erythromycin, clindamycin), oral antibiotics (tetracycline, minocycline, erythromycin, doxycycline, trimethoprim-sulfamethoxazole), and isotretinoin (Helms et al., 2006)</td>
<td>Induced by both topical (Roberts, 2003) and oral treatments. Resistance found in P. Acnes (Swanson, 2003) and both oral (Roberts, 2003) and intestinal flora (Valtonen et al., 1976). Patients and family members (Adams et al., 1985) affected. Resistant varieties appear transmissible between acne-prone individuals (Ross et al., 2003)</td>
</tr>
<tr>
<td>Blistering skin diseases</td>
<td>Rosacea</td>
<td>1.1 million outpatient visits per year, <a href="http://www.ncbi.nlm.nih.gov/pubmed/1153491">www.ncbi.nlm.nih.gov/pubmed/1153491</a></td>
<td>20.49% of patients use tetracyclines (Romanowicz et al., 2008)</td>
<td>NA (noninfectious)</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>Cholera</td>
<td>“Virtually eliminated.” <a href="http://www.cdc.gov/nzved/dbmd/disease_list/cholera">http://www.cdc.gov/nzved/dbmd/disease_list/cholera</a> gi.html (assume avg ∼ 0)</td>
<td>Cholera can be simply and successfully treated by immediate replacement of the fluid and salts lost through diarrhea. Antibiotics shorten the course and diminish the severity of the illness, but they are not as important as rehydration</td>
<td>Rare, but emerging in some parts of the world. <a href="http://www.cdc.gov/nczved/EID/vol8no3/01-0258.htm">http://www.cdc.gov/nczved/EID/vol8no3/01-0258.htm</a></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Syphilis</td>
<td>36,000 cases of syphilis in 2006, including 9,756 cases of primary and secondary (P&amp;S) syphilis. <a href="http://www.cdc.gov/std/syphilis/STD">www.cdc.gov/std/syphilis/STD</a> Fact-Syphilis.htm</td>
<td>Penicillin, other antibiotics if patient is allergic (doxycycline, tetracycline, and erythromycin)</td>
<td>None reported. <a href="http://www.cdc.gov/std/treatment">http://www.cdc.gov/std/treatment</a></td>
</tr>
<tr>
<td>Organism/Condition</td>
<td>Common Name</td>
<td>U.S. Cases per Year</td>
<td>Treatments</td>
<td>Resistance to Tetracycline</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> Alternative treatment</td>
<td>“Stomach ulcer”</td>
<td>Each year there are 500,000 to 850,000 new cases of peptic ulcer disease and more than 1 million ulcer-related hospitalizations (assume avg = 1M)</td>
<td>Tetracyclines are not first-line treatment for <em>H. pylori</em>. Multidrug therapies are more effective (Mirbagheri et al., 2006). Tetracycline is a suggested component in some combination therapies. <a href="http://www.helico.com/treattherapy.html">www.helico.com/treattherapy.html</a></td>
<td>Not found in the United States. <a href="http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=132778">http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=132778</a></td>
</tr>
<tr>
<td><em>Mycobacterium marinum</em> Alternative treatment</td>
<td>Fish tank granuloma</td>
<td>Estimated annual incidence is 0.27 cases per 100,000 adult patients (assume avg = 824). <a href="http://www.emedicine.com/med/topic1538.htm">www.emedicine.com/med/topic1538.htm</a></td>
<td>This organism is sensitive to rifampin, ethambutol, tetracyclines, trimethoprim-sulfamethoxazole (TMP-SMX), clarithromycin, and levofloxacin</td>
<td>Not significant. <a href="http://www.ncbi.nlm.nih.gov/pubmed/12153378?dopt=Abstract">http://www.ncbi.nlm.nih.gov/pubmed/12153378?dopt=Abstract</a></td>
</tr>
<tr>
<td><em>Mycobacterium fortuitum</em> Alternative treatment</td>
<td>Found in natural and processed water sources, as well as in sewage and dirt</td>
<td>From 1993–1996, 4.65–5.99 cases per million persons were reported to the CDC (Fritz and Woeltje, 2007) (assume avg ∼ 1,623)</td>
<td>Prolonged antibiotic therapy is generally required for <em>M. fortuitum</em> infection. Many antibiotics used. Because doxycycline has activity against only approximately one-third of isolates, generally not used as part of initial empiric regimen</td>
<td>Rates of resistance up to 50% have been reported. <a href="http://prod.hopkins-abxguide.org/pathogens/bacteria/mycobacteria/mycobacterium_fortuitum.html?contentInstanceId=255909">http://prod.hopkins-abxguide.org/pathogens/bacteria/mycobacteria/mycobacterium_fortuitum.html?contentInstanceId=255909</a></td>
</tr>
<tr>
<td><em>Burkholderia</em> species Alternative treatment</td>
<td>Glanders and melioidosis (bioweapon?)</td>
<td>A few isolated cases per year. <a href="http://www.cdc.gov/nczved/dfbmd/disease_listing/melioidosis">http://www.cdc.gov/nczved/dfbmd/disease_listing/melioidosis</a> GL.html (assume avg = 3)</td>
<td><em>Burkholderia pseudomallei</em>, the organism that causes melioidosis, is usually sensitive to imipenem, penicillin, doxycycline, amoxicillin-clavulanic acid, azlocillin, ceftazidine, ticarcillin-vulanic acid, ceftriaxone, and aztreonam</td>
<td>Resistance genes possibly widespread. <a href="http://www.jstage.jst.go.jp/article/jsme2/22/1/22_44/article">http://www.jstage.jst.go.jp/article/jsme2/22/1/22_44/article</a></td>
</tr>
<tr>
<td><em>Donovania granulomatis</em> Alternative treatment</td>
<td>Donovanosis (STD)</td>
<td>Fewer than 100 cases are reported annually, many of which are thought to be due to foreign travel. <a href="http://www.emedicine.com/derm/topic172.htm">http://www.emedicine.com/derm/topic172.htm</a> (assume avg = 100)</td>
<td>The recommended antibiotic is either trimethoprim/sulfamethoxazole or doxycycline. Alternatives include ciprofloxacin, erythromycin, or azithromycin</td>
<td>Rare. <a href="http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1194766">http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1194766</a></td>
</tr>
<tr>
<td>Epididymitis Alternative treatment</td>
<td>Scrotal infection, various causes</td>
<td>Incidence is less than 1 case in 1,000 males per year</td>
<td>Variety of antibiotics. <a href="http://www.emedicine.com/emerg/topic166.htm">http://www.emedicine.com/emerg/topic166.htm</a></td>
<td>Indeterminate (many infectious and noninfectious causes)</td>
</tr>
</tbody>
</table>
which high resistance rates to tetracyclines (an alternative treatment) have been observed.

The potential hazard from each of these three conditions is assessed in more detail next.

8.3.3. Tetracycline Resistance Hazards in Treating Periodontal Disease

Systemic antibiotics, including tetracyclines, are used to treat a subset of cases of severe gingivitis or chronic periodontal disease. Lundergan (2003) describes these cases as “aggressive” or “refractory” periodontitis, and notes that tetracycline hydrochloride, doxycycline, metronidazole, clindamycin, ciprofloxacin, amoxicillin/clavulanic acid, metronidazole in combination with amoxicillin, and metronidazole with ciprofloxacin have all been previously used. Greenstein (2000) provides the same list of potential systemic antibiotics. Both authors note the need for species identification and prior susceptibility testing before selecting an antibiotic to maximize effectiveness of treatment. The wide variety of bacteria (more than 500) identified within periodontal pockets, even when narrowed to only those specifically associated with periodontal disease, are still quite diverse. For example, for A. actinomycetemcomitans–associated periodontitis, researchers recommend that clinicians use amoxicillin with clavulanic acid and metronidazole. If the patient is allergic to penicillin, ciprofloxacin could be substituted for amoxicillin with clavulanic acid. Ciprofloxacin is effective against enteric rods, pseudomonads, and staphylococci. Another antibiotic that is effective and specific for anaerobes is clindamycin (Greenstein, 2000). At the same time, Greenstein concludes that systemic antibiotic therapy is usually not needed and should be avoided in routine treatment.

Although tetracycline resistance in bacteria associated with periodontal disease may be induced by treatment, it is unclear to what extent such resistance translates into treatment failures. Kleinfelder et al. (1999) found in their study of subgingival plaque microorganisms that tetracycline resistance rates among the major species identified ranged from 3 to 29%. However, the MICs for every sample were well below the concentration achievable in gingival crevicular fluid, implying that treatment could still succeed. Rodrigues et al. (2004) found that locally or systemically administered tetracycline resulted in a temporary selection of subgingival species intrinsi-
doxycycline ranged from 26% to 63% in a study by Swenson et al. (1985). Therefore, doxycycline is not recommended as a first-line treatment in the absence of susceptibility testing.

Given this information, it is unlikely that there are any tetracycline (doxycycline) resistance-related treatment failures of Mycobacterium fortuitum infections in the United States. Doxycycline is not used unless the infection is known to be susceptible, and several better alternatives exist. If there are no tetracycline resistance-related treatment failures, then the risk of such treatment failures caused by animal uses of tetracyclines would be zero.

### 8.3.5. Tetracycline Resistance Hazards in Treating Acne

The Merck Manual (Merck, 2008) recommends oral antibiotics, in conjunction with topical antibiotics, for patients with moderate acne. For these patients, “tetracycline is usually a good first choice.” Doxycycline and erythromycin are recommended as second-line agents. Nontetracycline treatments are recommended for other acne patients, including: topical clindamycin and benzoyl peroxide gels for mild inflammatory acne; oral isotretinoin for severe acne; and triamcinolone for cystic acne.

### 8.3.6. Historical Tetracycline Usage and Resistance for Acne in the United States and England

Tetracyclines have been used to treat millions of cases of acne in the United States for decades. Stern (2000) showed 5.1 million prescriptions of oral antibiotics (both new and renewals) for acne alone between 1996 and 1998 in the United States—approximately 2,876,000 women and 2,220,000 men. The data provided for women’s use of oral antibiotics show that just over a third of the prescriptions were for tetracyclines, broken down as: 13% for minocycline, 14% for tetracycline, and 7.5% for doxycycline. This extensive tetracycline use in human medicine is generally considered to have caused the spread of tetracycline-resistant strains of Propionibacterium acnes, the bacterium that causes infectious acne (Tan and Tan, 2005).

The risk of tetracycline-resistant acne for individual patients depends on many variables (e.g., age, stress, skin type, and so forth), but has not been associated with animal uses of antibiotics. (For example, a PUBMED search of “acne growth promoter” returns no hits.) One possible way to investigate whether use of tetracycline in animals might contribute significantly to human tetracycline-resistant acne cases is to compare resistance rates in human patients from locations with and without such use. (Such “ecological” comparisons may not support valid causal inferences, but can nonetheless be useful in identifying differences that can then be investigated more thoroughly by other methods, such as time series analysis.) Eady et al. (2003) performed a comprehensive evaluation of study data on resistance of P. acnes to antibiotic treatments, and concluded that overall prevalence rates for skin colonization with tetracycline resistant strains were “as high as 30%” in the United States. This is very consistent with a study of acne patients in the United Kingdom, which estimated that about 26.4% had tetracycline resistant P. acnes (Ross, 2003). Tetracyclines have not been used as growth promotion STAs in the United Kingdom for nearly four decades (since the early 1970s). Thus, it appears that substantial reservoirs of resistant P. acnes are created and maintained by other (non-STA) uses (presumably including treatment of human patients).

A second way to search for possible hazards is to examine longitudinal data, e.g., how much have treatment failures increased as animal antibiotic use and tetracycline resistance have increased? Again, detecting correlated increases does not by itself establish causality, but it may indicate a pattern worth investigating more carefully via time series analysis, quasi-experimental designs, or other causal analysis techniques. Del Rosso and Kim (2009) describe the increase in tetracycline resistance among acne patients over the past 40 years as reducing the effectiveness of tetracycline as a treatment option: “Over the past 4 decades, as the sensitivity of Propionibacterium acnes to several oral and topical antibiotics has decreased, the efficacy of oral tetracycline and erythromycin has markedly diminished, leading to increased use of doxycycline, minocycline, and other agents, such as trimethoprim/sulfamethoxazole.” On the other hand, Simonart et al. (2008) reported that, despite the increases in antibiotic resistance between 1962 and 2006, “oral tetracycline formulations displayed no change in efficacy” for the treatment of acne vulgaris. Thus, compounds in the tetracycline family (especially doxycycline) are still effective. Moreover, the increase in resistance due to human use has been large enough to prompt development of several alternative therapies, described next.
8.3.7. Alternatives to Tetracyclines and Changing Prescription Practices

Despite their heavy historical use in treating acne, tetracyclines are becoming regarded by many clinicians as less desirable than other approaches for treating most acne cases, in both the United States and Europe. For example, Kertzman et al. (2008) noted: “The 1999 practice guideline ‘Acne vulgaris’ from the Dutch College of General Practitioners has been revised. Benzoyl peroxide and local retinoids are first choice in local treatment of acne. When treatment with oral antibiotics is indicated, doxycycline is first choice. Use of minocycline is not recommended in general practice. It is recommended that both local and oral antibiotics are always combined with local benzoyl peroxide or a local retinoid.” A recent clinical trial in England concluded: “Topical antimicrobial therapies performed at least as well as oral antibiotics in terms of clinical efficacy. Benzoyl peroxide was the most cost-effective and minocycline the least cost-effective therapy for facial acne. The efficacy of all three topical regimens was not compromised by pre-existing propionibacterial resistance. Benzoyl peroxide was associated with a greater frequency and severity of local irritant reactions. It is suggested that the use of a combination of topical benzoyl peroxide and erythromycin gives less irritation and better quality of life” (Ozolins et al., 2005, emphasis added).

Clindamycin is becoming increasingly popular in place of erythromycin and tetracycline. Guay (2007) reported that “Clindamycin appears to be superior in efficacy compared with erythromycin and tetracycline,” and other investigators have recently recommended a combination clindamycin and benzoyl peroxide topical gel as highly effective, popular with patients, and not associated with bacterial resistance (e.g., Langner et al., 2008; McKeage and Keating, 2008). Thus, it appears that future prescriptions may shift away from oral tetracyclines toward topical clindamycin and benzoyl peroxide gels. In the United States, there has also already been a significant shift away from antibiotic therapies toward topical retinoids and oral isotretinoin (Thevarajah et al., 2005).

In summary, although tetracycline resistance in P. acnes poses a real risk of reduced efficacy of initial treatment, this risk appears to be caused primarily by the existence of a large, easily transmitted reservoir of tetracycline-resistant P. acnes, which, in turn, results from human use of tetracyclines to treat acne. Tetracycline use in food animals has never been identified as contributing to the risk of tetracycline-resistant P. acnes. To the contrary, comparing data from the United States and the United Kingdom, and examining longitudinal data in the United States, suggests that human use suffices to maintain a pool of tetracycline-resistant P. acnes, and that tetracycline STA use has had no known incremental impact on the efficacy of tetracyclines in treating acne vulgaris. Based on these observations, we conclude that there is no empirical evidence suggesting that treatment of human acne cases is compromised by use of tetracyclines in food animals.

8.4. From Qualitative Hazard Assessment to Quantitative Bounds on Risks from Tetracycline Resistance in Human Medicine

Our qualitative review of the potential tetracycline resistance hazards in Table I suggests that tetracycline STA use presents minimal or no risks to human health, as each condition is either noninfectious (blistering skin diseases and rosacea), has indeterminate causes (epididymitis and prostatitis), has no apparent relation to tetracycline use in food animals (acne, periodontal disease, and prostatitis), or is due to a bacterium for which resistance to tetracyclines is not observed (all others). However, for this last category, absence of evidence of resistance (and of resistance-related treatment failures) is not necessarily evidence of complete absence of resistance. It is only evidence that, if there is resistance, it is too rare to have been detected (so far). To obtain a rough upper bound on the greatest level of unobserved resistance risk that could be consistent with the absence of observed cases, suppose that tetracycline resistance does exist for some of the conditions in Table I that lack observed resistant cases. The total estimated average annual number of cases from the 22 such conditions listed in Table I is 1,888,659.5, of which most (1,800,000) are from atypical pneumonia strains and Helicobacter pylori. Tetracycline resistance status is known only for patients for whom samples were analyzed or tetracycline was actually prescribed. To get order-of-magnitude estimates of possible resistance risk, suppose that at least 20% of each condition leads to tetracycline prescriptions and/or resistance screening that would reveal tetracycline resistance if it were present; and assume that at least 20 years of observations are available, during which tetracyclines have been used in both human medicine and agriculture. (In reality, both 20% and...
20 years are low estimates for atypical pneumonia strains, for which tetracycline is the usual treatment, but these values suffice to illustrate the bounding calculation.) Then the total number of cases in which resistance could have been observed, if it were present, from all 22 conditions, is about: (1,888,659.5 cases per year) * (0.20 fraction observed) * (20 years), or roughly $7.6 \times 10^6$ observed cases without resistance.

An approximate 95% upper confidence limit for the true but unknown value of a proportion, based on 0 observed cases in N binomial trials, is $3/N$—the so-called rule of three for estimating risks when no occurrences have been observed (and $N > 30$) (Eypasch et al., 1995). For $N = 7.6 \times 10^6$, this formula yields an estimated 95% upper confidence limit of $3/(7.5 \times 10^6) = 4 \times 10^{-7}$ for the fraction of resistant (but as-yet-undetected) cases. (Departures from the binomial model to allow a mixture of cases with different resistance rates would reduce the variance around the mean rate (Feller, 1968, p. 231). This could perhaps reduce the upper confidence limit further, but we use the binomial model for simplicity, and because, among all models, it maximizes variance for a given mean. Also, the estimated upper bound of $4 \times 10^{-7}$ applies only as long there is no large change in historical rates. However, more detailed modeling of resistance dynamics in other contexts suggests that a history of decades of widespread use without resistance emerging makes it unlikely that a sudden jump will occur (Cox and Popken, 2004). For an individual selected at random from the U.S. population of approximately 300 million, an approximate upper 95% confidence limit for the probability of a tetracycline-resistant illness in a 70-year lifetime, from any of the 22 conditions eliminated from further consideration in Table I, is:

$$\left(\frac{70}{100,000,000}\right)\left(\frac{3}{1,888,659.5}\right)\left(\frac{0.2}{20}\right) = 1.75 \times 10^{-7}.$$

(Note that any uncertainties about the 1,888,659.5 number cancel out in this calculation, as it appears in both the numerator and the denominator.) The maximum-likelihood estimate, based on 0 observed resistant cases is, of course, 0. Even if such a case were to occur, the probability that it would be prescribed tetracycline (e.g., 20%, in these illustrative calculations), times the probability that resistance would result in treatment failure (which may be very small, e.g., less than 5%, based on other tetracycline-resistant infections that nonetheless respond to tetracycline therapy), times the probability that the resistant case is attributable to animal use of tetracyclines, rather than to human use (an unknown fraction, but perhaps not more than 1%, due to the much more direct effect of human use on human resistance), would further reduce the estimated risk to humans specifically from animal use of tetracycline (e.g., from $\leq 1.75 \times 10^{-7}$ lifetime risk of a tetracycline-resistant infection to perhaps $\leq 1.75 \times 10^{-11}$ lifetime risk of treatment failure due to a tetracycline-resistant infection caused by animal use of tetracycline). Even with the uncertainties and speculations inherent in such calculations, it seems clear that the rough order of magnitude of human health risks from tetracycline use in animals is not large. If a ban on continued use were to reduce the risk from $1.75 \times 10^{-11}$ to zero, the net effect would be to prevent only perhaps one treatment failure every two centuries, under current conditions.

9. TETRACYCLINE RESISTANCE IN THE ENVIRONMENT

Tetracycline-resistant bacteria are ubiquitous in the environment, with or without animal antibiotic use (e.g., Gebreyes et al., 2006), although animal antibiotic use certainly selects for resistant strains. For example, in the United States, tetracycline- and tylosin-resistant bacteria are found in manure from swine farms that are not using antimicrobials, as well as in field soils where manure is applied regularly; the prevalence does not differ among farms using versus not using antimicrobial feed additives for growth promotion (Chander et al., 2006). Smith et al. (2007) reported that resistance of E. coli to tetracycline, sulfonamides, and streptomycin is common in broiler chickens whether or not they receive antibiotics. Similarly, a European study by Heike et al. (2006) found that the diversity of tetracycline resistance genes in soils augmented with pig manure was independent of the levels of antibiotic use at the originating farms; they concluded that there is a considerable pool of resistance genes in soils.

Not surprisingly, tetracycline use does select for tetracycline-resistant bacteria in the environment. For example, Chee-Sanford et al. (2001) found a gradient in tetracycline-resistance genes in ground
water, with the diversity and quantity of resistance genes decreasing with distance from large, unlined pig manure lagoons. Peak et al. (2007) confirmed that tetracycline usage in cattle feedlots is associated with increased levels of tetracycline resistance genes in ground water. Resistance gene abundance was highly seasonal, 10–100 times greater in the fall than in the summer. Engemann et al. (2008) analyzed the survivability of tetracycline resistance genes in cattle feedlot wastewater and found that resistance genes disappeared at a rate of 71% per day in sunlight, and 51% per day in darkness. They also found significant variation in the rates for different resistance genes. \( \text{tet}(W) \) and \( \text{tet}(M) \) had the longest half-lives—on the order of hours.) This study, and related work summarized in Graham (2005), indicates that tetracycline resistance is developed at the point of use rather than in the environment. Further, resistance die-off in aquatic systems is generally very rapid, especially in light-exposed systems.

Taken together, these findings suggest that tetracycline use in animals selects for tetracycline-resistant bacteria in manure, soil, and water; even without animal antibiotic use, however, tetracycline resistance is widespread.

10. DISCUSSION AND CONCLUSIONS

Tetracycline drugs are important in human medicine, as well as in veterinary medicine. However, assessing each of several specific suggested threats to human health from use of tetracyclines as STAs—both indirect threats, from co-selection of MRSA or MDR Salmonella; and direct threats, from infection of human patients with tetracycline-resistant zoonotic bacteria (Table I)—suggests that reducing tetracycline use in food animals in the United States should not be expected to cause any improvements in human health or to reduce risks of antibiotic-resistant infections. The best point estimate of the human health risk of treatment failures caused by animal use of tetracycline, based on the evidence reviewed in previous sections, is: zero incremental tetracycline treatment failures per year in the United States (to several significant digits). However, the possibility of a risk that is too small to have been observed as yet (e.g., on the order of 0 to \( 1.75 \times 10^{-11} \) excess treatment failures per 70-year lifetime, due to a tetracycline-resistant infection caused by animal use of tetracycline) cannot be ruled out.

In part, the extremely small or zero risk of excess treatment failures is due to the fact that tetracyclines are not used to treat food-borne zoonotic illnesses such as campylobacteriosis, salmonellosis, or \( E. \) coli infections. In part, it is because, other than acne, there are few or no resistance-related treatment failures of tetracycline prescriptions used in human medicine in the United States (see Table I). For acne, human use suffices to maintain a reservoir of resistant \( P. \) acnes bacteria (as shown by historical experience in Europe), and there is no evidence that tetracycline use in animals contributes to this pool. Finally, although tetracycline resistance is common in both MRSA and MDR Salmonella, it appears from recent data (Gebreyes et al., 2006), that MDR cassettes that include tetracycline resistance are selected by other pressures, and not by tetracycline use per se. Time series analyses indicate that both community-acquired and hospital-acquired MRSA are driven by use of human antibiotics in hospitals.

Potential human health benefits from continued use of tetracyclines and other antibiotics in food animals cannot easily be quantified. Although antibiotic-free (ABF) and organic farms have been reported to have higher prevalence rates than conventional farms of bacteria such as \( \text{Campylobacter} \) in poultry (Luangtongkum et al., 2006) and Salmonella in pigs (Gebreyes, 2008) (but lower prevalence of \( \text{Campylobacter} \) in pigs, Hurd et al., 2008), it is not yet known to what extent, if any, these bacteria affect human health. Moreover, resistance rates for several antibiotics and bacteria are higher in bacteria isolated from conventional farms than in bacteria from ABF farms (ibid). For some other (nontetracycline) antibiotics, a comparison of these two potential effects (smaller microbial loads, increased proportion of resistant bacteria) suggests that the potential human health benefits due to reduced bacterial loads may outweigh by more than 1,000-fold the potential risks due to increased resistance (Cox and Popken, 2002, 2004), but similar calculations cannot be made for tetracycline STAs, as tetracycline is not used to treat zoonotic illnesses in the United States.

In Europe, growth promotion STA bans were initially estimated to have increased mortality rates in pig production, associated with scouring and proliferative enteritis, by 10%–15%, and these increases persisted for years (Hughes and Heritage, 2004; Cox and Ricci, 2008). If morbidity rates in pigs increased by a similar percentage due to withdrawal of tetracyclines and other STAs, then the initial results of Hurd et al. (2008), showing a significant positive correlation between decreased animal health (indicated by subclinical lesions) and increased microbial loads of
Campylobacter and Enterococcus on carcasses, might provide a causal mechanism by which reducing animal antibiotic use could account for some of the observed increases in campylobacteriosis (Lawley, 2007) and other zoonotic infections in Europe. To make this (or other) causal conjecture less speculative, it would be desirable to carry out more detailed time series analyses of changes in illness rates, microbial loads, and resistance fractions in isolates from animals, food, and people, as data become available. Denmark has led the way in collecting and publishing such data, and similar data are now being collected in other countries.

Without speculating further on causal mechanisms and potential human health benefits from continued use of animal antibiotics, it seems clear that there is no empirical support for concerns that continued use of tetracycline STAs in the United States will increase human health risks due to tetracycline-resistant illnesses. Some salient threats (e.g., from terrorist-produced tetracycline-resistant anthrax, or of prolonged courses of oral antibiotic therapy for tetracycline-resistant acne) are unlikely to be affected by any changes in animal antibiotic use. (Terrorists may use resistant anthrax regardless of animal antibiotic use, while routine use of tetracycline to treat moderate acne cases already provides an ample reservoir of tetracycline-resistant bacteria, for which other treatments are available.) Other resistance threats are also minimal because of the absence of significant numbers of tetracycline-resistance-related treatment failures (Table 1).

Current urgent political calls to ban tetracycline and other approved animal antibiotic uses, in an effort to protect human health, are framed in terms of a mental model of cause and effect in which bans would reduce contamination of family meals with “deadly” antibiotic-resistant pathogens or “super-bugs,” thereby reducing the risk of untreatable foodborne illnesses and deaths (Slaughter, 2008). Our review of data for specific illnesses suggests that this mental model has little relation to reality. Foodborne bacteria are not unstoppable or “deadly” except under rare, serious medical conditions, most commonly involving immunocompromised patients, that are not caused by animal antibiotic use. A more realistic mental model appears to be that, in the United States, as in Europe:

1. Reducing animal antibiotic uses that prevent animal illness and promote their health and growth would not reduce (but might increase) microbial loads and human bacterial illness rates;

2. Reducing STA uses in animals would not reduce antibiotic resistance rates in human infections (but might increase them, especially if more antibiotics important in human medicine become used for therapy instead of prevention) (Casewell et al., 2003); and

3. The very real and serious threats of MRSA and MDR “super-bugs” in human patients can be addressed effectively only by changing the use of antibiotics in human medicine.

Our analysis suggests that risk management policies based on these principles are far more likely to achieve intended public health benefits than are policies based on the belief or assumption that STA uses in animals contribute significantly to resistance risks in humans (Slaughter, 2008).

ACKNOWLEDGMENTS

We thank Alpharma and Phibro Animal Health for supporting the research reported here. We thank Dr. Jerry Mathers of Alpharma for useful discussions of recent literature and trends in resistance risks. The research questions addressed, methods and models applied, and conclusions reached are solely those of the authors.

REFERENCES


FDA-CVM. (US Food and Drug Administration, Center for Veterinary Medicine). Guidance for Industry # 152: Evaluating the safety of antimicrobial new animal drugs with regard to...
Assessing Potential Human Health Hazards and Benefits from Subtherapeutic Antibiotics


Helms RA, Herfindal ET, Quan DJ, Gourley DR. Textbook of Therapeutics: Drug and Disease Management. Lippincott Williams & Wilkins, 2006.


Lorian V. Antibiotics in Laboratory Medicine. Lippincott Williams & Wilkins, 2005.


Smith JL, Drum DJV, Daj Y, Kim JM, Sanchez S, Maurer JJ, Hofacre CL, Lee MD. Impact of antimicrobial usage on antimicrobial resistance in commensal Escherichia coli strains


