Human Health Risk Assessment of Penicillin/Aminopenicillin Resistance in Enterococci Due to Penicillin Use in Food Animals

Louis Anthony (Tony) Cox, Jr.,1,2,* Douglas A. Popken,1,3 and Jeremy J. Mathers4

Penicillin and ampicillin drugs are approved for use in food animals in the United States to treat, control, and prevent diseases, and penicillin is approved for use to improve growth rates in pigs and poultry. This article considers the possibility that such uses might increase the incidence of ampicillin-resistant Enterococcus faecium (AREF) of animal origin in human infections, leading to increased hospitalization and mortality due to reduced response to ampicillin or penicillin. We assess the risks from continued use of penicillin-based drugs in food animals in the United States, using several assumptions to overcome current scientific uncertainties and data gaps. Multiplying the total at-risk population of intensive care unit (ICU) patients by a series of estimated factors suggests that not more than 0.04 excess mortalities per year (under conservative assumptions) to 0.14 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 AREF infections among ICU patients. These calculations suggest that current penicillin usage in food animals in the United States presents very low (possibly zero) human health risks.

KEY WORDS: Animal antimicrobials; enterococcus; penicillin; resistance; risk assessment

1. INTRODUCTION

Penicillin drugs (specifically, Penicillin G, Procaine subtype) are approved for use in food animals in the United States to treat, control, and prevent diseases and to improve growth rates (FDA-CVM, 2007; Sechen, 2006; AHI, 2006). Concerns have been expressed that penicillin use might increase the risk of antibiotic resistance in human enterococcal infections from nonhuman sources, leading to increased morbidity and mortality (WHO, 2005, 2007; FAO/WHO/OIE, 2008). Approved feed usages of penicillins in food animals have been a controversial topic for several decades in the United States, with many reviews and initiatives undertaken to address resistance concerns (IOM, 1989; FDA, 2000; FDA, 2003). Regulatory approvals have been given for administration to animals via drinking water and feeds for therapeutic uses, including disease prevention and control, as well as for feed efficiency/growth promotion uses in food animals (FDA-CVM, 2007). The amounts of penicillins sold for use in food animals in the United States remain relatively low compared to other antimicrobials, with sole growth promotion uses representing a small subfraction of the total (AHI, 2006). Penicillin drugs have been...
identified as “critically important” to animal health (FAO/WHO/OIE, 2008).

The only penicillin drug type approved for non-therapeutic uses in the United States is Penicillin G (Procaine subtype), which is given primarily to swine and chicken; none is given to cattle. A USDA (2002) survey indicated that, in grower/finisher pigs, over 99.5% of all penicillin is administered (primarily via injection) for disease treatment and prevention. A relatively small amount of ampicillin is also used for disease treatment. In a large-scale study of 82 poultry farms in the eastern United States, Hayes et al. (2004) measured resistance levels of enterococci found in chicken litter. E. faecalis represented 53% of the isolates and had 0% penicillin resistance. E. faecium represented 31% of the isolates. Seventy-one percent of the E. faecium (71 out of 104 isolates) had penicillin resistance, but only 1% (1 out of 104) had ampicillin resistance.

This article quantifies the potential for continued use of penicillin drugs in food animals to harm human health by increasing the number of ampicillin-resistant enterococcal infections in human patients. After summarizing relevant background for the hazard of greatest concern—infec tions of intensive care unit (ICU) patients with ampicillin-resistant Enterococcus faecium (AREF) bacteria—the following sections focus on quantifying the fraction of such resistant infections that might be prevented by discontinuing the use of penicillin drugs in food animals.

2. BACKGROUND, HAZARD, IDENTIFICATION, AND SCOPE: REDUCING AMPICILLIN-RESISTANT E. FAE CULUM INFECTIONS IN ICU PATIENTS

Enterococci are commensal gram-positive bacteria found in the intestinal flora of most healthy birds and mammals, including people (Biavasco et al., 2007; Willems, 2000). In humans, enterococci typically comprise not more than 1% of the microflora of adults (FDA-CVM, 2004) and are normally harmless; however, they can cause opportunistic infections in ICU patients or others with weakened immune systems. The Enterococcus genus has 17 species, but most human clinical isolates are either E. faecalis (74–90%) or E. faecium (5–16%) (Varman et al., 2006).

E. faecalis infections are responsible for most clinical enterococcal infections, but penicillin (or ampicillin) resistance is rare in E. faecalis isolates from food animals and almost nonexistent in E. faecium isolates from retail meats (Hayes et al., 2003, 2004; McGowan et al., 2006; NARMS, 2005); none of the meat-borne E. faecalis samples isolated from retail meats in a national surveillance program (NARMS, 2002–2005) exhibited resistance to penicillin. Furthermore, ampicillin remains highly effective against clinical E. faecalis (Jones et al., 2004). Therefore, our risk assessment focuses on the identified hazard of ampicillin resistance among human E. faecium infections.

Risk to human health arises because some strains of enterococci may become opportunistic pathogens, potentially resistant to multiple drugs, that infect patients who are already seriously ill (typically in ICUs) with immune systems weakened by organ transplants, chemotherapy, AIDS, or other causes. Indeed, enterococcal infection is the second most common hospital-acquired infection in the United States (Varman et al., 2006). These infections can prolong illness and increase patient mortality. Vancomycin-resistant enterococci (VRE) are of particular concern because of their virulence and resistance to even some recently developed antibiotics. Vancomycin-resistant E. faecium (VREF) can cause serious and often fatal disease in vulnerable populations, such as liver transplant patients and patients with hematologic malignancies (Leavis et al., 2003; Rice, 2001).

Many enterococcal infections, including VRE, resolve without antimicrobial treatment (Varman et al., 2006; Rice, 2001). In severe cases for which antimicrobial treatment is provided, penicillin and ampicillin are often the leading choices. Other drugs that are also effective against human enterococcal infections include gentamicin, vancomycin, quinupristin-dalfopristin (Synercid®), linezolid (Zyvox®), tigecycline (Tygaci1®), and nitrofurantoin. These can be used in patients with allergy or high-level resistance to penicillin and ampicillin. Many ampicillin-resistant cases can also be treated successfully with high doses of ampicillin, either alone or in combination with drugs such as gentamicin or streptomycin (Varman et al., 2006; Murray, 2000).

Most E. faecium infections in ICU patients in the United States are now resistant to vancomycin (Edmond et al., 1999; Jones et al., 2004; Leavis et al., 2003). Patients with VREF have worse outcomes than those with vancomycin susceptible strains—longer hospital stays and higher mortality (Webb et al., 2001). As noted by Rice (2001), virtually all VREF are also ampicillin resistant: “More
than 95% of VRE recovered in the United States are *E. faecium*; virtually all are resistant to high levels of ampicillin.” Hence, our risk assessment treats VREF as being (at least approximately) a subset of AREF. One suggested explanation is “that the close association of the vancomycin and ampicillin resistance phenotypes, at least in VanB-type VRE, is explainable by their inclusion within large, transferable genetic elements” (Hanrahan et al., 2000, p. 1350). However, widespread ampicillin resistance appeared in 1982 (Fortun et al., 2002), while vancomycin resistance appeared in the early 1990s in *E. faecium* (Murray, 2000).

Since most VREF are AREF (although many AREF are not VREF), and assuming that changes in animal penicillin use would not significantly affect vancomycin resistance (consistent with historical data), we focus on human (ICU patient) infections with vancomycin-susceptible strains of AREF. Presumably, this is the subpopulation that might experience decreased ampicillin resistance if discontinuing animal penicillin drugs were to replace some AREF cases with ampicillin-susceptible cases. For patients with VREF, we assume that AREF would persist (due to the observed co-occurrence of AREF in VREF strains), so that no benefit from reduced AREF would be achieved for these patients.

The following sections seek to quantify potentially preventable AREF cases and the human health benefits that might be created if these AREF cases were prevented (made ampicillin-susceptible) by discontinuing penicillin drug uses in food animals. This approach draws on recent advances in sequencing technology that enable more precise strain groupings and epidemiological analyses than have previously been possible.

### 3. METHODS AND DATA: UPPER BOUNDS FOR PREVENTABLE MORTALITIES

Recognizing that a farm-to-fork (forward chaining) approach is not practical for AREF due to data and knowledge gaps in release, exposure, and dose-response relations, we instead start with more readily available human data on ICU case loads and resistance rates, similar to the approach in Cox and Popken (2004). We then work backward to estimate a plausible upper bound on the annual number of human patient mortalities that might be prevented by discontinuing penicillin use in food animals.

For purposes of conservative (i.e., upper-bound) risk assessment, we define a potentially preventable mortality to occur whenever the following conditions hold: (1) an ICU patient dies, following (2) an *E. faecium* infection that (3) is resistant to ampicillin (AREF) (and hence might have benefited had ampicillin resistance been prevented). The infection was (4) vancomycin-susceptible (and hence might have also been ampicillin-susceptible, had it not been for penicillin use in food animals); (5) not known to have been contracted from the hospital environment (and hence might have been prevented by actions external to the hospital, such as elimination of AREFs from food animals); (6) could have come from food animals (i.e., has a genotype or resistance determinants of the types found in food animals). (7) The patient tolerated penicillin (i.e., was not allergic, and hence might have benefited from ampicillin, had it not been for resistance). We propose that the conjunction of these seven conditions should be interpreted as necessary for a mortality to have been caused (with nonnegligible probability) by resistance due to use of penicillin in food animals, even though it is not sufficient (e.g., the infecting strain might have had some other origin than food animals, or the patient might have died anyway, even if the infection had been ampicillin-susceptible).

Accordingly, the following sections estimate a plausible upper bound on annual preventable mortalities from AREF infections based on the following product of factors:

\[
\text{Preventable AREF mortalities per year} \leq (\text{total number of ICU infections per year}) \times (\text{fraction caused by } E.\ faecium) \times (\text{fraction of ICU } E.\ faecium\ infections\ that\ are\ AREF\ and\ exogenous,\ i.e.,\ not\ known\ to\ be\ of\ nosocomial\ origin}) \times (\text{fraction of these exogenous AREF cases that are vancomycin-susceptible}) \times (\text{fraction of vancomycin-susceptible exogenous AREF cases that might have come from food animals}) \times (\text{excess mortality rate for AREF cases compared to ASEF cases}).
\]

That is, we first quantify the expected annual number of AREF cases in the United States that might benefit from ampicillin treatment if food animal uses of penicillin were halted (i.e., cases that are penicillin-tolerant and vancomycin-susceptible and that might have been caused by resistance determinants from food animals). Then, we multiply this number by the excess mortality rate for resistant as opposed to susceptible cases.

### 3.1. Estimated Number of ICU Infections Per Year

Enterococcal infections are generally limited to already hospitalized individuals. *E. faecium*
infections are frequently associated with nosocomial bloodstream infections occurring within ICUs. A recent FDA risk assessment for virginiamycin (FDA-CVM, 2004) provided the following two approximate estimates:

(1) \( N = \) annual number of ICU infections = 104,372.5 based on blood-stream infections.
(2) \( N = 315,000 \) based on septicemia cases.

The study does not weight these alternatives. To be conservative (i.e., to maximize estimated risks), we will use the larger estimate, \( N = 315,000 \) cases/year. (Patients with severely complicated urinary tract infections (UTIs) are also sometimes treated with intravenous antibiotics, including combinations of gentamicin and ampicillin, but ceftriaxone may be substituted for ampicillin if needed, and oral antibiotics (e.g., trimethoprim, cephalosporins, nitrofurantoin, or ciprofloxacin) are used in the vast majority of cases (http://adam.about.com/reports/000036_7.htm). We therefore do not include UTI cases in this assessment.)

### 3.2. Fraction of ICU Infections Caused by \( E. \ faecium \)

The proportion of ICU infections that are caused by \( E. \ faecium \) can be estimated with the help of the following two fractions from the same FDA-CVM study:

(1) \( P_{\text{ent}} = 0.10 \) = fraction of ICU infections caused by Enterococcus. (Wisplinghoff et al., 2004 provide an estimate of 0.09. To be conservative, we use the higher estimate of 0.10.)
(2) \( P_{\text{EF,ent}} = 0.25 \) = fraction of enterococcal infections caused by \( E. \ faecium \).

The product of these two factors, \( f_{\text{EF}} = P_{\text{ent}} \times P_{\text{EF,ent}} = 0.025 \), is the estimated fraction of ICU infections caused by \( E. \ faecium \). An approximate value for the expected annual rate of \( E. \ faecium \) infections can then be obtained via the equation:

\[
\text{Expected annual number of } E. \ faecium \text{ infections} = N \times f_{\text{EF}} = N \times P_{\text{ent}} \times P_{\text{EF,ent}} = 315,000 \times 0.025 = 7,875 \text{ } E. \ faecium \text{ infections/year.}
\]

### 3.3. Fraction of ICU \( E. \ faecium \) Infections that are Ampicillin-Resistant and Exogenous (Nonnosocomial)

Most AREF infections are contracted nosocomially. Indeed, it is possible that few or none originate in food animals. For example, as stated by Kuhn et al. (2005), in Europe “it seems that animal-associated VRE probably reflect the former use of avoparcin in animal production, whereas VRE in human-associated samples may be a result of antibiotic use in hospitals.” Since nosocomial transmission is a hospital-specific problem that can often be eliminated by rigorous control measures, we restrict our risk assessment to exogenous (nonnosocomial) cases that are potentially attributable to food animals. (If this restriction is dropped in sensitivity analysis, the effect is simply to divide estimated annual impacts by the nonnosocomial fraction of cases, which increases them approximately sixfold.)

Cox and Popken (2004) used data from several studies in the 1990s to estimate an approximate mean value of 0.17 for the fraction of exogenous cases in the United States. (This is the mean of a range of values, extending from a low of 0.089 based on data in Bischoff et al. (1999) to a high of 25% based on estimates in Austin et al. (1999).) More recent investigations of the molecular epidemiology of drug-resistant \( E. \ faecium \) infections suggest that, if anything, this proportion may have decreased since the 1990s as a particular hospital-adapted clone of \( E. \ faecium \) called CC17 has spread widely in hospitals in the United States and elsewhere (Leavis et al., 2006; Top et al., 2007; Willems, 2001). Approximately 88% of \( E. \ faecium \) isolates from hospital outbreaks (n = 32) belong to Complex-17, compared to 59% of all clinical isolates (n = 162). 21% of all isolates (n = 315) are hospital-associated strains. (Wisplinghoff et al., 2004 provide an estimate of 0.09. To be conservative, we use the higher estimate of 0.10.)

\[
N \times f_{\text{EF}} = N \times P_{\text{en}} \times P_{\text{EF,ent}} = 315,000 \times 0.025 = 7,875 \text{ } E. \ faecium \text{ infections/year.}
\]
per nonoutbreak case. In summary, the estimated expected annual number of ampicillin-resistant, exogenously caused (i.e., nonnosocomial) *E. faecium* infections in the United States is no more than:

\[(7,875 \text{ } E. \text{ faecium } \text{infections/year}) \times (0.17 \text{ nonnosocomial fraction}) \times (0.187 \text{ ampicillin-resistant fraction}) = \frac{7,875 \times 0.17 \times 0.187}{1} = 250 \text{ exogenous AREF infections per year.}\]

### 3.4. Fraction of Vancomycin-Susceptible Cases

Assuming that almost all vancomycin-resistant strains of *E. faecium* in the United States are also ampicillin resistant (but not vice-versa) (Rice, 2001), the relatively recent data of Jones *et al.* (2004) show that, in the United States, about 14% of *E. faecium* strains are ampicillin resistant and vancomycin susceptible. Specifically, 90.3% of *E. faecium* isolates were resistant to ampicillin and 76.3% of *E. faecium* isolates were resistant to vancomycin. The difference is 0.903 – 0.763 = 0.14. This is an estimate of the fraction of *E. faecium* isolates that are AREF but not VREF—in other words, the vancomycin-susceptible AREF of interest for our risk assessment. Thus, 0.14/0.903 = 0.155 is the estimated fraction of AREF that are vancomycin susceptible. Using this point estimate yields:

\[
\text{Expected exogenous ampicillin-resistant and vancomycin-susceptible cases per year} \leq 250 \times 0.155 = 38.75 \text{ vancomycin-susceptible AREF infections/year.}
\]

This should be considered an upper bound. For example, research by Suppola *et al.* (1999) suggested that Van A and Van B *E. faecium* incorporate into an endemic vancomycin-susceptible AREF strain.

### 3.5. Fraction of Exogenous Cases Potentially from Food Animals

As reviewed above, genetic similarities between ampicillin-resistant strains found in nonoutbreak *E. faecium* infections among hospitalized patients (most of which carry the *esp* virulence gene and other distinctive genes) and strains found in food animals (most of which do not) is weak (Kuhn *et al.*, 2005; Leavis *et al.*, 2006, 2007). No clear empirical attribution of hospital cases to food animals can be made based on these data.

Fig. 1 summarizes data that suggest a possible upper-bound quantitative estimate for the contribution of strains of *E. faecium* found in food animals to strains found in nonoutbreak (non-Complex-17) human patient isolates. The figure represents inferred patterns of evolutionary descent among multiple strains of *E. faecium*. Each number represents a sequence type (ST). Lines connect STs that differ in only one of seven “housekeeping genes.” The relative sizes of the circles represent the relative prevalences of the STs. In the relatively few cases where human patient and food animal (pig and poultry) clusters overlap, the strains falling in the overlap might have come from a common environmental source (e.g., soil or water), or might be due to a “reverse causation” flow from humans to pigs via surface water, flies, pets, or other paths (Guardabassi & Dalsgaard, 2004; Macovei & Zurek, 2006; Rodrigues *et al.*, 2002).

The Multi Locus Sequence Typing website (www.mlst.net—curator: Rob Willems) provides a database of 490 *E. faecium* samples—a subset of those used to generate Fig. 1 of Leavis *et al.* (2006). The data indicate 87 unique STs among “Clin˙Isol” and “Hosp˙Surv” (human, nonoutbreak, noncommunity) clusters. (We do not consider the “Hosp˙Outbreaks” category, since these are assumed to fall into the nosocomially transmitted group. We also do not consider the “Human˙comm” category as these are noninfectious strains found in healthy individuals.) Two of these 87 STs (26 and 32) are shared with poultry and four (5, 6, 18, 133) are shared with pigs. If we assume, conservatively, that all shared types represent transmission from food animals to human patients (rather than from people to animals, or to both from common environmental sources such as soil, water, flies, or birds), then an estimate of the fraction of strains in human patients that might originate in food animals is: 6/87 = 0.069. This assumes that all shared types arise from foodborne transmission of resistant bacteria, originating in food animals on the farm, to people via the food chain. Using this point estimate reduces the above estimate to:

\[
\text{Expected exogenous vancomycin-susceptible and ampicillin-resistant cases per year from food animals} \leq (38.75 \text{ exogenous vancomycin-susceptible and ampicillin-resistant cases per year}) \times (\text{fraction of not more than } 6/87 \text{ from food animals}) \leq 2.67 \text{ exogenous vancomycin-susceptible and ampicillin-resistant infections per year from food animals.}
\]

### 3.6. Penicillin Allergies

Hospitalized patients who are allergic to penicillin cannot have their enterococcal infections treated with penicillin or ampicillin. Since such patients are not harmed by penicillin resistance, we need to exclude them from risk calculations. A large U.S. study of hospitalized patients requiring
antimicrobials found that 15.6% reported an allergy to penicillin (Lee et al., 2000). (This exceeds the average in the general population, which is expected.) The remaining \(1 - 0.156 = 0.844\) of patients corresponds to:

\[
\text{Expected exogenous vancomycin-susceptible ampicillin-resistant cases per year from food animals, in penicillin-tolerant patients} = 0.844 \times 2.67 = 2.25.
\]

3.7. Excess Mortalities

The next step is to calculate the increase in human health harm—especially, increased mortality—among the 2.25 expected cases per year calculated in the previous steps. Fortun et al. (2002) reported no statistically significant differences in outcomes between ampicillin-resistant cases and ampicillin-susceptible cases. They stated that:

There were no significant differences in the outcome of patients with ampicillin-resistant and -susceptible strains. We did not find significant differences in mortality between the two groups. Overall mortality in patients with bacteraemia caused by ampicillin-resistant and -susceptible \(E. \text{faecium}\) was 34% and 21%, respectively (OR: 2.1; 95% CI: 0.47–9.95). Mortality attributed to bacteraemia was 21% and 15%, respectively (OR: 1.5; 95% CI: 0.27–8.85). (Fortun et al., 2002, p. 4)

To obtain a nonzero risk estimate despite the reported absence of statistically significant differences in mortality, we make the conservative assumption that the numerical difference in bacteraemia-attributed mortality rates between patients with...
ampicillin-resistant and -susceptible strains reflects a true causal effect (i.e., that resistance does cause a 21% – 15% = 6% increase in absolute mortality risk, per patient per infection). In other words, we treat the statistically nonsignificant difference as a true difference caused by ampicillin-resistance (but acknowledge that this is not the original authors’ interpretation and that the true difference could be as small as zero). This assumption provides a possible basis for calculating a nonzero human health risk from ampicillin resistance.

With this assumption, the expected annual excess mortality risk caused by ampicillin resistance becomes:

Expected excess mortalities per year (for the entire U.S. population) caused by exogenous vancomycin-susceptible and AREF infections, assumed to originate from food animals, in penicillin-tolerant patients ≤ 2.25 \times 0.06 = 0.135 excess mortalities/year.

In reality, annual mortality risks from AREF are likely to be much smaller than this, as patient-cultured isolates would typically be screened for resistance prior to treatment (standard procedure indicated for such infections) and then patients with AREF would be treated with other drugs such as gentamicin, vancomycin, quinupristin/dalfopristin, linezolid, daptomycin, tigecycline, or nitrofurantoin. In addition, the above mortality estimate does not address morbidity or quality-adjusted life years (QALYs) lost due to potentially preventable resistance. The patients at risk are already severely ill (usually, immuno-compromised) patients such as leukemia, transplant, and AIDS patients. Thus, the hypothesized increased risk (per infection with ampicillin-resistant vancomycin-susceptible *E. faecium*) represents fewer QALYs lost than would be the case for otherwise healthy patients. We have therefore not attempted to quantify QALY impacts.

4. RESULTS SUMMARY, SENSITIVITY AND UNCERTAINTY ANALYSIS

Table I summarizes key parameter estimates, calculations, assumptions, and resulting risk estimates from this study. It is traditional in presenting point estimates to also present interval estimates to inform decisionmakers about the plausible range of estimated values. In the present analysis, however, the key uncertainties have little to do with statistical sampling error, and are not adequately characterized by confidence limits. Rather, they arise from uncertainty about the validity and conservatism of the assumptions in Table I.

Qualitatively, the main uncertainty is about whether there is a nonzero risk to human health from animal use of penicillin drugs. We have assumed that there is, but there is no clear empirical proof that the risk is nonzero. To bridge this knowledge gap, Table I incorporates several conservative qualitative assumptions that jointly imply that the risk is nonzero. Other quantitative parameter values presented, and their implied risk estimate of \leq 0.135 excess mortalities/year, are intended to be realistic, data-driven values (rather than extreme upper bounds or 95% upper confidence limits) contingent on these conservative qualitative assumptions.

The most important conservative elements in Table I are the following qualitative assumptions:

1. Transfer of ampicillin resistance from food animal bacteria to bacteria infecting human patient occurs. The assumption that ampicillin-resistant strains and/or determinants are transferred from strains in food animals to human ICU patients is fundamental to the assessment in Table I. Such transfer has never been shown to occur, but may be possible, based on the similarities described in Fig. 1.

2. Withdrawing animal drug use would immediately and completely prevent the problem. Table I assumes that halting penicillin use in food animals would immediately eliminate all ampicillin resistance from the cases in Table I. This is a deliberately extreme assumption. In reality, halting use might have little or no impact on the already very low levels of ampicillin resistance.

3. Resistance increases patients mortality. The assumption that ampicillin resistance causes an increase in the mortality rates of the patients in Table I is made even though, in reality, no statistically significant difference in mortality rates has been found between resistant and nonresistant cases (Fortun et al., 2002).

With these assumptions, the calculations in Table I predict that excess mortalities per year in the entire U.S. population could be as high as 0.135, i.e., an excess mortality expected roughly once every seven to eight years, if current conditions persist. This risk is concentrated among ICU patients already at high risk of such infections. With less conservative assumptions, the estimated risk falls to about 0.04 excess mortalities per year, i.e., about one
excess mortality every 25 years in the United States under current conditions. The multiplicative calculation in Table I makes sensitivity analysis of these results to changes in the values of specific factors especially straightforward: the final risk estimate is directly proportional to each factor listed.

The more conservative risk estimate of 0.135 excess mortalities per year equates to an average individual risk rate in the most at-risk group (ICU patients) of approximately 0.135/315,000 = 4.3 × 10^{-7} excess mortalities per ICU patient. For the U.S. population as a whole, this corresponds to an average individual risk of 0.135/300E6 = 4.5 × 10^{-10} excess fatalities per person-year, or a lifetime risk of about 80(6 × 10^{-10}) = 3.6 × 10^{-8} excess risk of mortality per lifetime (for an assumed 80-year lifetime). This is well below the risk level of 1 × 10^{-6} (1 per million lifetimes) sometimes cited as a threshold for concern for carcinogens in the environment. If the less conservative risk estimate of 0.04 excess mortalities per year is used, these individual and population risks are reduced by a factor of 0.04/0.135, or more than threefold. If one or more of the key qualitative assumptions listed above are violated, then the true risk could be as low as zero.

We have emphasized that the most important uncertainty in this analysis is discrete—is the preventable fraction of risk positive or is it zero?—and that such uncertainty is not well characterized by a confidence interval. Nonetheless, it may be useful to consider a rough upper bound on how large the true risk might be. A crude estimate is given by Markov’s inequality for nonnegative random variables if we assume that the risk estimates in Table I represent expected values. In this case, a (possibly extreme) upper bound on the true but unknown risk is that it has at most a 5% probability of exceeding the point estimates (0.135 or 0.04 excess mortalities per year) by more than 20-fold. To the extent that these point estimates are biased upward by the assumptions listed in Table I, upper bounds based on Markov’s inequality will be even more conservative.

### Table I. Summary of Risk Calculation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Base Case Value</th>
<th>Possible Alternative Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N = \text{ICU infections/year}$</td>
<td>$N = 315,000$</td>
<td>$N = 104,372.5$</td>
<td>FDA-CVM, 2004</td>
</tr>
<tr>
<td>$P_{\text{ent}} = \text{fraction of ICU infections caused by Enterococcus}$</td>
<td>0.10</td>
<td>0.09 (Wisplinghoff et al., 2004)</td>
<td>FDA-CVM, 2004</td>
</tr>
<tr>
<td>$P_{\text{EF,ent}} = \text{fraction of enterococcal infections caused by } E. \text{faecium}$</td>
<td>0.25</td>
<td></td>
<td>FDA-CVM, 2004</td>
</tr>
<tr>
<td>Fraction of enterococcal infections caused by $E. \text{faecium}$ that are exogenous (nonnosocomial)</td>
<td>$\leq 0.17$</td>
<td></td>
<td>Cox and Popken, 2004.</td>
</tr>
<tr>
<td>Fraction of exogenous cases that are ampicillin resistant</td>
<td>0.187</td>
<td></td>
<td>Willems et al., 2005</td>
</tr>
<tr>
<td>Fraction of exogenous ampicillin-resistant cases that are vancomycin susceptible</td>
<td>0.155</td>
<td></td>
<td>Jones et al., 2004</td>
</tr>
<tr>
<td>Fraction of exogenous ampicillin-resistant vancomycin-susceptible cases possibly from food animals</td>
<td>0–0.069 (0.069 assumed)</td>
<td></td>
<td>Data of Leavis et al., 2006</td>
</tr>
<tr>
<td>Fraction of exogenous ampicillin-resistant cases with penicillin-tolerant host</td>
<td>0.844</td>
<td></td>
<td>Lee et al., 2000</td>
</tr>
<tr>
<td>Fraction of these cases that would become ampicillin susceptible if penicillin use in food animals were terminated</td>
<td>0.00–1.00. (1 is assumed)</td>
<td></td>
<td>Conservative assumption</td>
</tr>
<tr>
<td>Increase in mortality risk per case, due to ampicillin resistance</td>
<td>0.00–0.06. (0.06 is assumed)</td>
<td></td>
<td>Fortun et al., 2002, conservative assumption</td>
</tr>
<tr>
<td>RISK $\leq 0.14$ potential excess mortalities/year</td>
<td>315000 × 0.10 × 0.25 × 0.17 × 0.187 × 0.155 × 0.00–1.00. (1 is assumed)</td>
<td></td>
<td>Product of preceding factors</td>
</tr>
<tr>
<td></td>
<td>$0.135$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$0.04$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. DISCUSSION AND CONCLUSIONS

Concerns about penicillin use in food animals and potential transfer of resistance to humans have
been debated over several decades. However, current knowledge and data, as analyzed in Table I, suggest that ongoing penicillin usage in food animals in the United States creates at most quite minor mortality risks to human health. Quantitatively, it appears that these risks are unlikely to exceed one potentially preventable mortality in the U.S. population roughly every 7–25 years. The true value could be smaller (and is zero if any of our key conservative qualitative assumptions are incorrect).

Removing penicillin drugs from the animal drug market is a possible risk management option (and has actually been proposed). But significant baseline resistance among antibiotic-free animals (Patton et al., 2006), along with small potential human health benefits even if removal immediately eliminated all preventable cases of resistance in human patients (as Table I assumes) suggests that even complete product removal would not detectably improve human health. Increased surveillance of food-animal-associated enterococci and tracking their penicillin and ampicillin resistances (NARMS, 2005), as well as compliance with judicious use guidelines for practitioners and producers (AVMA, 2008), may suffice to protect human health against the current small risks without compromising the health of food animals.

ACKNOWLEDGMENTS

We thank Alpharma for supporting the research reported here. The research questions addressed, methods and models applied, and conclusions reached are solely those of the authors.

REFERENCES


