Antibiotics have dramatically improved our capacity to treat infectious diseases of bacterial origin. Indicative of their importance in human medicine is that they are the second most prescribed class of drugs in the United States (McCaig and Hughes). However, such extensive use is a mixed blessing. Antibiotics belong to a class of resources that lose efficacy with use (Tisdell), because each antibiotic treatment triggers natural selection pressures that result in some reduction in bacterial susceptibility to the drug. That is, resistance increases with use. Thus, antibiotic use in human medicine jointly generates a positive private good—the increase in the probability of recovery of the patient—and a negative externality—the reduction in bacterial susceptibility and a corresponding decrease in future drug efficacy.\footnote{We abstract from the reduction in rates of infection associated with antibiotic use to focus on long-term issues.}

Drug susceptibility has a strong common property nature because the effect of each individual’s use on the development of resistance is minimal. Therefore, agents generally ignore the impact that their actions have on resistance, which tends to lead to overuse.

The standard remedy for externalities caused by overuse is to reduce use through taxes or other restrictions. In the case of antibiotics, reductions in use might have to take account of the fact that large amounts of antibiotics are used in animal production. Externalities can be caused by the use of antibiotics in animal production if reductions in bacterial susceptibility due to use of antibiotics in animal production are transmissible to humans. If such transmission occurs, then efforts to combat antibiotic resistance should be extended to livestock use.

The objective of this study is to investigate simultaneously the trade-offs between present and future antibiotic use both in human medicine and in livestock production. We focus on the use of antibiotics as growth promoters in the animal industry because this is the area of controversy. We develop a dynamic optimal control model that includes both human and animal use of antibiotics and their possible impacts on antibiotic susceptibility. We identify the time path of optimal human use and animal use, and, in particular, we obtain the conditions under which a ban on subtherapeutic use of antibiotics in animal production may be warranted, and the conditions that support repeal of a ban.

Analyzing human and animal use jointly is useful because in the debates between the animal industry and human health professionals there is a tendency to blame each other for the rise in antibiotic resistance. The most obvious example of this conduct concerns the dispute on the proportion between human and animal use of antibiotics. Table 1 reports summary estimates of three different studies on antibiotic use in the United States. The most widely reported figures are those of the 1989 Institute of Medicine report, which evaluated that in 1985 over half of the total antibiotic production was used for growth promotion in the livestock industry. In a more recent study, the Animal Health Institute, which represents
Table 1. Three Estimates of Human and Animal Antibiotic Use, in Million Pounds

<table>
<thead>
<tr>
<th></th>
<th>Human Use</th>
<th>Total Animal Use</th>
<th>Subtherapeutic Animal Use</th>
<th>Total Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institute of Medicine, 1989</td>
<td>13.9</td>
<td>18.0</td>
<td>16.1</td>
<td>31.9</td>
</tr>
<tr>
<td>(1985 values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal Health Institute, 2000</td>
<td>32.2</td>
<td>17.8</td>
<td>3.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Union of Concerned Scientists,</td>
<td>4.5</td>
<td>30.6</td>
<td>27.6</td>
<td>35.1</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The crucial issue in the debate over the potential for conflicts between human and animal use of antibiotics is the degree of transmissibility of resistance from animals to humans. There are two main processes through which transmission could occur. The first is direct transmission through the food chain. Quantifying the importance of this effect is difficult because this entails following the bacteria from the animal to the food processing industry to the infected individual. However, one study exists that traces infectious agents through the food chain (Mølbak et al.) and one tracks down on-farm transmission (Fey et al.).

The second, and possibly more important, process is the indirect transmission of resistance via commensals (nonharmful bacteria) and in general through the environment. This transmission channel conceivably presents the greater danger because “the exchange of genes is so pervasive that the entire bacterial world can be thought of as one huge multicellular organism in which the cells interchange their genes with ease” (Levy, p. 49). The leakage of antibiotics into ecosystems has been characterized as an environmental problem (Morris, O’Brien, Summers). Quantifying this effect is even more difficult than tracking transmission through the food chain. However, the information currently available has induced the World Health Organization to recommend that the use of any antimicrobial agent for growth promotion in animals should be terminated if it is used as a human therapeutic or if it is known to select for cross-resistance to antimicrobials used in human medicine (World Health Organization).

Even though our understanding of the dynamics of resistance development is incomplete, it is clear that antibiotic resistance is fast becoming a critical problem both in the community and in the hospital. Very few new antibiotics are being developed and resistance has developed to all known antibiotics (Gold and Moellering), indicating that the stock of available susceptibility is decreasing.

The basic framework of analysis in this paper is similar to that developed by Brown and Layton. The net benefits of human and animal use of antibiotics and the problem of optimal use are modeled in a dynamic setting, because antibiotic treatment today causes decreased effectiveness in the future. The human use part of the model is similar to that developed in Secchi and Babcock. We consider health status as an element of the individual’s utility function.

We model the effectiveness of the antibiotic (or susceptibility of the target bacteria to it) as a nonrenewable resource following the classical optimal pesticide use literature (see the seminal papers of Hueth and Regev, and Taylor and Hadley). In the case of bacteria, this modeling choice has a two-fold rationale. First, many resistant bacteria appear not to suffer from fitness costs (Stewart et al.). If fitness costs were present, then resistance could be treated as a renewable resource, because temporarily halting the use of the antibiotic would let the fitter susceptible bacteria take water samples from 139 streams across thirty states during 1999 and 2000. Veterinary and human antibiotics were found in almost 50% of stream samples.

2 No independent estimates exist besides the Institute of Medicine report. The United States Department of Agriculture estimates of antibiotic use in agriculture are limited to fruit and nut crops.

3 Some recent studies have started to tackle this issue. For example, Smith et al. present a model for the population prevalence of human commensal antibiotic-resistant bacteria and suggest that agricultural antibiotic use hastens the appearance of antibiotic-resistant bacteria in humans. An indirect indication of the effects of antibiotic use on the environment is given by a recent United States Geological Survey study (Kolpin et al.) that analyzed water samples from 139 streams across thirty states during 1999 and 2000. Veterinary and human antibiotics were found in almost 50% of stream samples.

4 By fitness cost we specifically mean a lower relative probability of survival and reproductive capacity.
over. Secondly, there is evidence that resistant bacteria that do have lower fitness are able to develop compensatory mutations through time that increase their fitness (Morell, Schrag and Perrot).

The Modeling Framework

As noted above, we limit the analysis to subtherapeutic antibiotic (STA) use in the animal industry. We assume that the dose of antibiotics is predetermined for both humans and animals. With respect to livestock use, subtherapeutic dose rates are quite low (200 grams per ton of feed), so even though there are indications that the development of resistance is dose dependent (National Research Council), the range of dose rates actually used is quite limited. We also assume heterogeneous benefits from STAs. Livestock production systems and producer management ability vary significantly. Evidence is mounting that STAs are substitutes for management effort (Hayes et al., National Research Council). Producers who use low levels of disease control practices obtain the greatest marginal benefits from STAs. This suggests that there are diminishing marginal returns to subtherapeutic use.

To capture diminishing returns, we characterize the number of animals being raised as $K$. Without loss of generality, we order the animals from the least efficiently managed to the most efficiently managed. If $k \in [0, 1]$ is the proportion of animals given subtherapeutics, then the net benefits from the use of the antibiotic are $g(k)$, such that $g'(k) > 0$, $g''(k) \leq 0$, $g(0) = G > 0$, where $G$ represents the returns for the least efficient farmer.

We normalize the size of the human population to one. Agents have identical endowments and Cobb-Douglas preferences over their income and their health. Health is a function of whether a patient is treated or not, the severity of the infection, and the efficacy of antibiotics. As we noted above, we assume that the choice of treatment is a discrete decision, because patients do not choose the dose of antibiotic but rather whether to seek treatment or not. We define treatment for individual $i$ as $e_i = 1$ and no treatment as $e_i = 0$. If an agent receives treatment, his health state $H_i$ is a function of the efficacy of the antibiotic (or the level of susceptibility). The effectiveness of the drug is represented by the concave function $f(E)$, where $E \in [0, 1]$ is the efficacy of antibiotics, or the stock of susceptibility. The higher the efficacy of the antibiotic, the closer the health state is to good health, $H$, so that $\lim_{E \to 1} f(E) = H > 0$, while $\lim_{E \to 0} f(E) = 0$. Efficacy $E$ can be seen as an approximation of the percentage of bacteria susceptible to antibiotics, and $f(E)$ then represents the effectiveness of antibiotics in treating the illness. If $E = 1$, any antimicrobial will be effective. As $E$ declines, the number of drugs that will treat the illness decreases as well. If an agent receives treatment, then $EU(Y, \theta_i, e_i = 1) = (Y - p)^a[f(E)]^{1-a}$, where $p$ is the price of antibiotics and $Y$ is income. For simplicity, we assume that antibiotic prices are constant and reflect production costs, and that agents cannot avail themselves of health insurance and have to pay for their antibiotic prescriptions in full.

If agents receive no treatment, their utility is a function of an exogenous parameter $\theta_i \in \mathbb{R}$, $\theta_i [0, 1]$, which represents the severity of the infection or the probability of recovering and being healthy. At $\theta_i = 0$, the infection is at its highest, and therefore the agent will certainly not recover, while at $\theta_i = 1$ the infection is not present and the agent is healthy. In the absence of treatment, utility is $EU^0(Y, \theta_i, e_i = 0) = (Y - p)^a[1 - f(E)]^{1-a}$, where $H > 0$ and $\theta \in [0,1]$. Agents will therefore opt for treatment as long as $EU^i(Y, \theta_i, e_i = 1) > EU^i(Y, \theta_i, e_i = 0)$ or $(Y - p)^a[f(E)]^{1-a} > (Y)^a(H \theta_i)^{1-a}$. Therefore, if antibiotic prices are not exorbitant, then agents in very poor health will still be better off receiving antibiotic treatment even when antibiotics have lost most of their efficacy.

The development of resistance is given by

$$ (1) \quad \dot{E} = -\omega \gamma - \epsilon k $$

where $\alpha$ is the marginal impact of individual usage on resistance development, $\gamma$ is the proportion of agents receiving treatment, and $\epsilon$ is the degree of transmissibility of resistance from animals to humans multiplied by the impact of individual animal use on resistance. This specification follows Brown and Layton in that the effect of antibiotic usage on the stock of susceptibility is linear. If $\epsilon = 0$, so that there is no transmissibility and/or effect of animal use on resistance, the choice of the optimal subtherapeutic dose is separate from that of human use. If, however, $\epsilon > 0$, then the magnitude of $\epsilon$ becomes an important determinant of the optimal policy. We do not include in the analysis the possibility of resistance being transferred from humans to animals because it is likely to be a third-order effect, and because we are not
focusing on therapeutic use of antibiotics in animals. Furthermore, there is evidence that “the emergence of resistance does not necessarily confer inefficacy on subtherapeutic antibiotic use.” (National Research Council, p. 77)

The Dynamics of Optimal Use

We assume that the time \( T \) at which a backstop becomes available is known. The backstop does not rely on the same stock of susceptibility as the existing drug, so the salvage value of susceptibility in human medicine at \( T \) is zero. The social planner seeks to maximize

\[
\max \int_0^T \left[ \int_0^\gamma E U^t(\text{treated}) + \int_\gamma^1 E U^t(\text{untreated}) + g(k) \right] e^{-rt} dt
\]

where \( r \) is the discount rate. Substituting the explicit utility functions described above we have

\[
\max \int_0^T \left[ \int_0^\gamma (Y - p)^a [f(E)]^{1 - \alpha} dx + \int_\gamma^1 (Y)^a (H_0)^{1 - \alpha} d\theta + g(k) \right] e^{-rt} dt.
\]

Solving the integrals

\[
\max \int_0^T \left[ (Y - p)^a [f(E)]^{1 - \alpha} x \left|_0^\gamma \right. + (Y)^a (H)^{1 - \alpha} \left( \frac{\theta}{2 - \alpha} \right)^{2 - \alpha} + g(k) \right] e^{-rt} dt.
\]

Therefore,

\[
\max \int_0^T \left[ (Y - p)^a [f(E)]^{1 - \alpha} \gamma + (Y)^a (H)^{1 - \alpha} \frac{1 - (\gamma)^{2 - \alpha}}{(2 - \alpha)^{2 - \alpha}} + g(k) \right] e^{-rt} dt.
\]

s.t. \( \dot{E} = -\omega \gamma - \varepsilon k. \)

The present value Hamiltonian is

\[
H = \left[ (Y - p)^a [f(E)]^{1 - \alpha} \gamma + (Y)^a (H)^{1 - \alpha} \frac{1 - (\gamma)^{2 - \alpha}}{(2 - \alpha)^{2 - \alpha}} + g(k) \right] e^{-rt} + \mu [-\omega \gamma - \varepsilon k].
\]

Since the proportion of agents and animals treated is bounded from above and below, we write these constraints as \( k \geq 0, -k \geq -1, \gamma \geq 0, \) and \( -\gamma \geq -1. \)

The Lagrangian for the problem is

\[
L = H + \lambda_1 k + \lambda_2 (-k + 1) + \lambda_3 \gamma + \lambda_4 (-\gamma + 1).
\]

The first-order conditions are

\[
0 = \frac{\partial L}{\partial \gamma} = (Y - p)^a [f(E)]^{1 - \alpha} - (2 - \alpha) \gamma f(E) e^{-rt} \gamma - \mu \omega + \lambda_3 - \lambda_4
\]

and

\[
0 = \frac{\partial L}{\partial k} = f'(k) e^{-rt} - \mu \varepsilon + \lambda_1 - \lambda_2
\]

with the complementary slackness conditions \( \lambda_1 \geq 0, \lambda_2 \geq 0, \lambda_3 \geq 0, \lambda_4 \geq 0, \) and \( \lambda_1 k = 0, \lambda_2 (-k + 1) = 0, \lambda_3 \gamma = 0, \lambda_4 (-\gamma + 1) = 0. \)

We will limit our analysis to interior solutions for human use, as they are the most policy-relevant ones. We can then write the shadow value of susceptibility as

\[
\mu = \frac{1}{\omega} \left\{ (Y - p)^a [f(E)]^{1 - \alpha} - (Y)^a (H)^{1 - \alpha} \frac{(\gamma)^{1 - \alpha}}{(2 - \alpha)^{2 - \alpha}} \right\} e^{-rt}.
\]

The transversality condition for \( E \) is \( E \geq 0, \) and \( \lim_{t \to T} E(t) \mu(t) = 0. \)

If \( p > 0 \), the human use of antibiotics will cease before the resource will be extracted completely.

Equation (8) characterizes the optimal level of treatment, at which the marginal net benefits of using the antibiotic, 0 = \( (Y - p)^a \times \left[ f(E) \right]^{1 - \alpha} - (Y)^a (H)^{1 - \alpha} \frac{(\gamma)^{1 - \alpha}}{(2 - \alpha)^{2 - \alpha}}, \) equal the marginal costs in terms of resistance development, \( \mu \omega. \) Equation (10) illustrates how the shadow value of susceptibility decreases over time because the resource becomes less and less effective.

To determine the time path of the optimal proportion of agents treated, we take the derivative of \( \mu \) with respect to time to obtain
Secchi and Babcock

For a ban as of susceptibility. We can rewrite the conditions less than the impact of use on the shadow value the marginal product of subtherapeutic use is 0 when the maximum (net) discounted value of  is 

Hence, we have that the time path for the optimal policy is to limit human use of antibiotics both across the population and through time.

As for the use of antibiotics in livestock production, (9) indicates that a ban will be optimal if \( g'(0) \) decreases. Consequently, there may be instances in which it is not optimal to ban the antibiotic in animals at all, and cases in which it becomes optimal to use older antibiotics in animal production.

Figure 1 illustrates the various factors the optimal policy depends upon. At \( t = 0 \), the initial shadow value of susceptibility for human medicine times the transmissibility coefficient \( \varepsilon \) determine the opportunity cost for subtherapeutic use. They need to be compared to the marginal benefits of STAs, \( g'(0) \). An initial ban is warranted in cases \( b \) and \( c \). In case \( b \), the ban is eliminated fairly soon, at time \( T^* \). In case \( c \), the ban is not removed until \( T^{**} \). In case \( a \), a ban is never optimal. The time frame of reference is important—no new antibiotics have been put on the market since the 1960s, though a new class is currently undergoing human trials. Moreover, no novel technologies have yet emerged that can substitute for antibiotics in human medicine (see Secchi and Babcock for
more details on this issue). Therefore, $T$ could be as long as 100 years. Equation (15) also highlights the importance of the effect of human use on resistance, $\omega$, particularly in comparison with $\varepsilon$. If the human impact on resistance is much higher than the animal one, the relative costs of subtherapeutic antibiotic use in terms of the resistance buildup will be lower. More studies are needed to accurately quantify all these elements.

When the number of animals treated becomes positive, its time path will depend on the same issues that determine the optimality of a ban. Assuming $0 < k < 1$, we have from (9) that $0 = f'(k)e^{-rt} - \mu\varepsilon$, and $\mu = f'(k)e^{-rt}$. We take the time derivative of $\mu$ and substitute in to find

$$\dot{\mu} = \frac{f''(k)k e^{-rt}}{\varepsilon} - r \frac{f'(k)e^{-rt}}{\varepsilon} < 0$$

(16) $$\dot{k} = -\varepsilon(1-\alpha)(Y-p)^\alpha[f(E)]^{-\alpha}f'(E) - r \frac{f'(k)}{f''(k)}.$$  

(17) 

The first part of (17) is positive: The number of treated animals will increase because the comparative productivity of STAs increases as the effectiveness of the drug in human medicine declines. The second part is negative, and it reflects the decrease in marginal productivity of an increased number of animals treated. The net effect cannot be determined without numerical simulations.

Conclusions

Our analysis indicates that to combat the excessive depletion of susceptibility, human use of antibiotics should be decreased below the level resulting from private optimization. There is growing evidence that the current level of human use is indeed leading to excessive resistance buildup. For example, the Centers for Disease Control and Prevention has established that around a third of the 150 million outpatient antibiotic doses prescribed each year are unneeded (as quoted in Levy).

Since transmissibility of resistance from human to human is proven, the overuse of antibiotics in human medicine is clearly suboptimal. On the other hand, if there is a positive degree of transmissibility of antibiotic resistance from animals to humans, then a ban on subtherapeutic antibiotic use might be justified, particularly if the majority of antibiotic use occurs in animal agriculture, as some reports suggest.

Specifically, our results imply that, if transmissibility is present, the decision to ban subtherapeutic antibiotic use will depend on the extent of transmissibility, the marginal benefits to livestock producers, and the corresponding costs of resistance in human medicine due to antibiotic use in animal production. In our analysis, we have assumed that all antibiotics contribute equally to resistance development. However, our results suggest that partial bans may be warranted for antibiotics of high value to human medicine. The model could be extended to include various types of antibiotics with different degrees of transmissibility. Our framework could then be used to determine which antibiotics might be subject to a ban.

The costs of a ban for the animal industry would not be insignificant. The benefits of subtherapeutic antibiotic use for the animal industry and the potential costs of a ban have been the subject of several studies. Mathews provides a comprehensive review of the existing literature. Most of the recent studies have focused on the swine sector. For example, according to Algozin, Miller, and McNamara, the net returns from subtherapeutic antibiotic use amount to $1.26 per pig. Brorsen et al., on the other hand, estimate the net benefits of using subtherapeutics to be $2.76 per hog. Finally, Hayes et al. use data from the Swedish and Danish experience in banning subtherapeutics to estimate the impact of such a ban in the United States. They find that the short-run cost increase would be $6.05/head, decreasing to $5.24 in the long run. No recent estimates exist of the effects of banning only some antibiotics from subtherapeutic use. Presumably, however, these costs would be substantially lower than the costs of a total ban, as long as a suitable alternative existed.

The costs of banning subtherapeutic antibiotic use would have to be counterbalanced against the benefits to human medicine, in terms of reduced buildup of resistance to antibiotics. The total human costs of antibiotic resistance are hard to quantify, because part of the costs occurs in the outpatient care sector, and there are few reports on the failure of the first lines of therapy and the cost of alternative treatment. The effect of antibiotic resistance on nosocomial infections is better known. According to the National Foundation for Infectious Diseases, in 1990, the costs of antibiotic-resistant nosocomial infections were as high as
$4 billion/year (reported in U.S. Congress, Office of Technology Assessment). The Office of Technology Assessment in 1995, on the other hand, put the floor on the nosocomial costs at $1.3 billion/year.

Further economics research is needed to understand the extent of excessive antibiotic use and the incentives mechanisms that might be used to curb it. In our analysis, we have assumed that the stock of antibiotics is given and that production costs are constant. Extensions of the model could consider the role of the pharmaceutical industry in using their market power to ration antibiotic use and in discovering both new antibiotics and alternative technologies whose effectiveness does not decrease with use, such as “biospecific antibodies,” which recognize harmful bacteria and take them to the human cells that can eliminate them (Nemecek).

References


