Streamlined Analysis for Evaluating the Use of Preharvest Interventions Intended to Prevent Escherichia coli O157:H7 Illness in Humans

James Withee, Michael Williams, Terry Disney, Wayne Schlosser, Nate Bauer, and Eric Ebel

Abstract

The U.S. Department of Agriculture Food Safety Inspection Service is responsible for ensuring the safety of meat, poultry, and egg products consumed in the United States. Here we describe a risk assessment method that provides quantitative criteria for decision makers tasked with developing food safety policies. To demonstrate the utility of this method, we apply it to a hypothetical case study on the use of an Escherichia coli O157:H7 cattle vaccine to prevent human illness caused by consuming beef. A combination of quantitative risk assessment methods and marginal economic analysis are used to describe the maximum cost per unit that would still allow the vaccine to be a cost-effective intervention as well as the minimum effectiveness it could have at a fixed cost. We create two economic production functions where the input is number of vaccinated cattle and the output is human illnesses prevented. The production functions are then used for marginal economic analysis to assess the cost/benefit ratio of using the vaccine to prevent foodborne illness. In our case study, it was determined that vaccinating the entire U.S. herd at a cost of between $2.29 and $9.14 per unit (depending on overall effectiveness of the vaccine) would be a cost-effective intervention for preventing E. coli O157:H7 illness in humans. In addition, we determined that vaccinating only a given fraction of the herd would be cost effective for vaccines that are less effective or more costly. For example, a vaccine costing $9.00 per unit that had a 100% efficacy but required 100% herd coverage for immunity would be cost effective for use in about 500,000 cattle each year—equating to an estimated 750 human illnesses prevented per annum. We believe this approach could be useful for public health policy development in a wide range of applications.

Introduction

The U.S. Department of Agriculture (USDA) Food Safety Inspection Service (FSIS) is responsible for ensuring the safety of meat, poultry, and egg products consumed in the United States (FSIS/USDA, 2008). The development of public health policies designed to reduce the burden of foodborne disease is often a complex task that requires difficult decisions be made with incomplete data. Here, we describe a streamlined approach to provide decision makers with quantitative economic “break-even” points to help inform decisions. This streamlined approach combines risk assessment and marginal economic methodologies.

Risk assessment provides decision makers and risk managers a scientific approach to evaluate the complex issues associated with foodborne illness. The main objective of risk assessment in a public health context is to provide estimates on the probability of disease occurrence given a particular policy decision. These estimates are then presented to policy makers and risk managers to help inform their decisions.

The simplest form of risk assessment provides a qualitative assessment based on available scientific literature, while more elaborate assessments usually include complex mathematical models. When resources and time are limited, choosing the most appropriate assessment method for the decision at hand is critical. Traditional quantitative microbial risk assessment models for foodborne illness are process models that include several steps from “farm to fork.” These models typically require substantial time and resources.

Economics has always played a separate and equally important role from risk assessment in the risk management decision process. Traditional benefit–cost analysis has been a primary tool for evaluating the cost effectiveness of potential risk mitigation strategies once the risk analysis was...
completed. Policies have been implemented when the expected benefits of the rule (i.e., avoided illnesses) equaled or exceeded the expected cost of policy implementation. In addition, economists have traditionally been responsible for economic welfare analysis of major proposed new rules. This second form of analysis focuses on determination of who were the economic winners and losers from any proposed policy change (Unfunded Mandates Reform Act of 1995; Regulatory Flexibility Act of 1980).

In this paper we present an approach that integrates economic analysis with risk assessment to provide decision makers with the economic feasibility of different alternatives at an earlier stage in the decision-making process. It emphasizes two factors that are important in a resource-constrained public policy environment: (1) the speed and efficiency of the analysis and (2) the usefulness of the results for the decision-making process. A case study is presented that applies this approach to the use of a hypothetical vaccine for *Escherichia coli* O157:H7 in cattle to reduce the rate of *E. coli* O157:H7 illness in humans caused by consuming beef.

*E. coli* O157:H7 is a serious illness estimated to affect approximately 70,000 people in the United States each year (Mead *et al.*, 1999). Symptoms range from severe diarrhea and fever to complications including hemolytic uremic syndrome (CDC, 2008c). Cattle are the primary reservoir for *E. coli* O157:H7, and bovine vaccines have recently been developed to help reduce human illness by lowering prevalence among cattle (Peterson *et al.*, 2007; McNeilly *et al.*, 2008; Smith *et al.*, 2008). We used the available literature to estimate parameters for a hypothetical vaccine and then estimate the relevant break-even points for decision makers—including the minimum effectiveness of a vaccine that still allows it to be cost effective at a fixed price, the maximum price allowable at a fixed effectiveness, and optimal levels of vaccine use at a fixed price and effectiveness. No specific cattle vaccine is referenced in this analysis nor should any implications with regard to available cattle vaccines be drawn.

To assess the cost effectiveness of an on-farm intervention such as vaccination, we first must define the relationship between the occurrences of the pathogen in slaughtered cattle and human illness cases. Another relationship is then defined between occurrences of the pathogen in slaughtered cattle and use of vaccine. These two relationships define a production function that describes the production of foregone human illnesses as a function of the input, vaccinated cattle.

In economics, marginal cost describes the change in cost associated with a change in an output produced. Derivation of marginal cost uses a production function that can be inverted to describe how a change in an input cost (e.g., vaccination) will change the output produced (e.g., number of human illnesses foregone).

Based on the principles of welfare maximization, an intervention may be considered cost effective as long as its marginal cost is less than or equal to the marginal benefit of a unit of production. For our purposes, a vaccination program is considered cost effective as long as the marginal cost of vaccination is no greater than the marginal benefit of a foregone human illness. We believe that this approach to defining quantitative break-even points will prove useful in many different contexts for decision makers and creators of public policy.

Methods

**Relationship between *E. coli* O157:H7 occurrence in slaughtered cattle and human illness**

We begin with the assumption that the prevalence of *E. coli* O157:H7 in cattle is related to the risk of illness from consuming beef. If $y$ is the annual number of beef-associated human *E. coli* O157:H7 illnesses and $x$ is the annual number of *E. coli* O157:H7–colonized cattle slaughtered in the United States, then we can define a relationship such that $y$ is some function of $x$ [i.e., $y = f(x)$]. If no *E. coli* O157:H7–colonized cattle were slaughtered in a given year, then we assert that no human illnesses caused by *E. coli* O157:H7 would occur; therefore, $f(0) = 0$. The following sections predict corresponding values for $x$ and $y$ given current conditions in the United States. Human illnesses per annum are estimated from available human health surveillance data and ancillary epidemiologic evidence. Colonized slaughter cattle are predicted from available prevalence data and slaughter counts.

**Human illnesses per annum, $y$.** Active surveillance of the U.S. population provides the best data for estimating the rate of *E. coli* O157:H7 illness. The Centers for Disease Control and Prevention operate the National Foodborne Disease Surveillance Network (FoodNet) in collaboration with the U.S. Department of Agriculture, the U.S. Food and Drug Administration, and various state public health departments. FoodNet provides active surveillance for foodborne diseases—including Shiga toxin–producing *E. coli*—in 10 sites across the United States. As of 2007, the population under FoodNet surveillance was approximately 45.5 million persons (15% of the U.S. population) in 10 states (CDC, 2008b). We first adjust reported *E. coli* O157:H7 FoodNet cases to account for the magnitude of under-reporting (Powell *et al.*, 2000). Under-reporting is predicted by the proportion of cases that seek medical care ($z_1$), the fraction of medical care cases that have a stool culture obtained ($z_2$), the fraction of stool cultures examined for *E. coli* O157:H7 ($z_3$), and the fraction of *E. coli* O157:H7 culture assays that correctly identify the pathogen ($z_4$). Reported cases are divided into those that experience bloody diarrhea ($\beta$) and those that do not ($1 - \beta$). Except for $z_4$, the under-reporting fractions are different for these two classes of cases. Subscripts differentiate the fractions such that $z_{1B}$ and $z_{1NB}$ signify the fractions of blood and nonbloody diarrhea cases that seek medical care, respectively (Ostroff *et al.*, 1989; Hedberg *et al.*, 1997).

Given the annual number of reported human *E. coli* O157:H7 cases ($N_{obs}$), we can estimate the actual number of these cases ($N_{true}$) as follows:

**Equation 1**

$$N_{obs} \left( \frac{\beta}{z_{1B}z_{2B}z_{3B}z_{4}} + \frac{1 - \beta}{z_{1NB}z_{2NB}z_{3NB}z_{4}} \right) = N_{true}$$

The average number of *E. coli* O157:H7 illnesses reported in FoodNet from 2000 through 2006 was 535 (CDC, 2008a). Adjusting for the population under FoodNet surveillance and the population of the United States, we estimate 3953 annual illnesses. Data from epidemiologic studies on unreported *E. coli* O157:H7 illnesses are summarized in Table 1 (Powell *et al.*,...
Table 1. Epidemiologic Data Used to Estimate the Number of Unreported O157:H7 Illnesses

<table>
<thead>
<tr>
<th></th>
<th>% Reported cases$^a$</th>
<th>% Ill seeking care$^b$</th>
<th>% Cultured by physician$^b$</th>
<th>% Tested for O157 at lab$^c$</th>
<th>Test sensitivity$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody diarrhea</td>
<td>85%</td>
<td>55%</td>
<td>78%</td>
<td>79%</td>
<td>75%</td>
</tr>
<tr>
<td>Nonbloody diarrhea</td>
<td>15%</td>
<td>8%</td>
<td>36%</td>
<td>47%</td>
<td>75%</td>
</tr>
</tbody>
</table>

$^a$Cieslak et al., 1997.  
$^b$Hedberg et al., 1997.  
$^c$CDC, 1997.


2000). Using the FoodNet reported illnesses and the epidemiological fractions from Table 1, we estimate the number of E. coli O157:H7 illnesses using Equation 1:

\[
3,953 \left( \frac{3,368}{(0.55)(0.78)(0.79)(0.75)} + \frac{585}{(0.08)(0.36)(0.47)(0.75)} \right) = 70,874
\]

To derive the annual cases attributed to beef consumption, we must determine the fraction of total cases caused by consuming beef. Outbreak surveillance data from the Center for Disease Control provide an estimate of the proportion of total E. coli O157:H7 illnesses that can be attributed to consumption of beef (CDC, 2008b). Outbreak data from 2000 through 2006 report 1949 E. coli O157:H7 illnesses. Of the 1435 illnesses attributed to one or more causes, 472 were attributable to consuming beef, or approximately 33%. Thus, an estimated 23,388 E. coli O157:H7 illnesses are caused in the United States each year from beef consumption. This estimate does not account for uncertainty inherent in the number of reported cases, outbreaks, or the epidemiological data used to estimate the unreported fraction, which have been reported elsewhere (Powell et al., 2000; Ebel et al., 2004).

Number of colonized cattle, x. The number of E. coli O157:H7–colonized cattle slaughtered each year is predicted by the prevalence of colonized slaughter cattle (π) and the total cattle slaughtered per year (M) (i.e., x = Mπ). USDA-FSIS data provide estimates of M; the 2004–2007 average is approximately 32 million total cattle slaughtered each year (FSIS/USDA, 2008).

Predictions from a risk assessment concerning E. coli O157:H7 in ground beef provide evidence about π (Ebel et al., 2004). This analysis predicted herd-level prevalence among feedlots (πF) and breeding herds (πB) in the United States. It also predicted within-herd prevalence levels (ωi) for each herd type during the summer (June–September) and winter (October–May) seasons. Given these components, we can determine π as follows:

\[
\pi = W_F \pi_F (W_i \omega_{F,i} + W_w \omega_{F,w}) + W_B \pi_B (W_i \omega_{B,i} + W_w \omega_{B,w})
\]

where \(W_F\) and \(W_B\) are the fractions of all slaughtered cattle that originate from feedlots and breeding herds, respectively. Further, \(W_i = 4/12\) and \(W_w = 8/12\) are seasonal weights for summer and winter, while \(\omega_{ij}\) is indexed for herd type and season.

Given estimates of the parameters in Equation 2 from Table 2, we calculate that \(\pi = 10\) and \(x = 32,000,000 \times 10 = 3.2\) million. Nevertheless, our estimate for π comprises substantial uncertainty given the limitations of available data.

Alternatives for \(y = f(x)\)

Given two points, \((0, 0)\) and \((x, y)\), where \((x, y)\) represents the status quo in the United States, we can posit an infinite number of relationships between x and y. Assuming that \(f(x)\) is monotonic increasing, we examine two simple theoretic relationships that can be used in this screening analysis.

We begin with a generic model for calculating the probability of illness per beef serving (\(P(ill)\)):

\[
P(ill) = P(exp) \int_{0}^{\infty} R(D)g(D)\,dD
\]

where \(P(exp)\) is the prevalence of contaminated servings, \(R(D)\) is a dose–response function and \(g(D)\) is the distribution of doses in contaminated servings at the point of consumption.

A linear relationship between \(x\) and \(y\) stems from the assumption that changes in \(P(exp)\) will not effect \(g(D)\). In this case, \(P(ill|exp) = \int R(D)g(D)\,dD\) is a constant value and \(P(ill) \propto P(exp)\). Further, given the total servings of beef consumed per year \((S)\): \(y = S \times P(ill)\).

If we consider each slaughtered animal as a composite of many servings of beef, then some fraction of servings are contaminated from the fraction of colonized cattle. It is likely that the prevalence of contaminated servings is substantially less than the prevalence of colonized live cattle, but the precise nature of this relationship is unknowable other than by complex modeling. Others have asserted a proportional relationship between live animal prevalence and proportion of contaminated servings (Hald et al., 2004; Bartholomew et al., 2005; Van der Fels-Klerx et al., 2008). Following that work, we

Table 2. Escherichia coli O157 Herd and Within-Herd Prevalence Estimates (Ebel et al., 2004)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Feedlots</th>
<th>Breeding herds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herd prevalence</td>
<td>88%</td>
<td>63%</td>
</tr>
<tr>
<td>Summer within-herd prevalence</td>
<td>22%</td>
<td>4%</td>
</tr>
<tr>
<td>Winter within-herd prevalence</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Fractions of cattle slaughtered</td>
<td>82%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Fractions of cattle slaughtered by class are estimated from Food Safety Inspection Service records (2004–2007).
assert that \( P(\text{exp}) = kx \), where \( k \) is less than 1. Therefore, \( y \propto x \) can be derived because

\[
y = S \times P(\text{ill}) \propto S \times P(\text{exp}) = \frac{Sk}{M} x
\]

A proportional relationship between \( x \) and \( y \) is easy to understand if, for example, herd prevalence is reduced but the dynamics of infection, carcass contamination and food handling are unchanged. In this case, we reduce the total number of colonized cattle but do not ultimately change the distribution of doses among contaminated servings; therefore, we expect a reduction in human illnesses directly proportional to the reduction in herd prevalence.

If we write Equation 3 in terms of \( x \) and \( y \) but now assume that the dose distribution at consumption \( g(D) \) is not independent of the number of colonized cattle slaughtered, then:

**Equation 4**

\[
y = \frac{Sk}{M} \left( \int_{x=0}^{\infty} R(D)g(D|x)\,dx \right) x = \frac{Skx}{M} P(\text{ill}|\text{exp}, x)
\]

and the functional relationship between \( x \) and \( y \) is not linear. Nevertheless, it is expected that an intervention that caused \( x \) to decrease/increase would also cause \( P(\text{ill}|\text{exp}, x) \) to decrease/increase (i.e., \( \partial P(\text{ill}|\text{exp}, x) / \partial x > 0 \)). If this is the case, then an increase in the number of colonized slaughter cattle will also increase the levels of contamination per contaminated serving. If we assume that \( P(\text{ill}|\text{exp}, x) \) is directly proportional to \( x \), then we have \( P(\text{ill}|\text{exp}, x) = ax \) and \( y \) is simply a power function of \( x \):

\[
y = \frac{Skx}{M} x^2
\]

The integral in Equation 4 is complex; typically, it would require substantial modeling to relate \( y \) and \( x \). Nevertheless, limited analysis suggests—by assuming \( g(D) \) is an exponential distribution and that its mean changes directly proportional to a change in live cattle prevalence—that \( P(\text{ill}|\text{exp}, x) \) changes proportionate to a change in \( x \).

For this analysis, we initially assume \( y = ax \), but also consider the implications of a nonlinear relationship, \( y = bx^2 \), where \( a \) and \( b \) are calculated based on the status quo values of \( (x, y) \) we previously developed. Therefore, \( a = y/x = 23,388/3.2 \text{ million} = 7.3 \times 10^{-3} \) and \( b = y/x^2 = 2.3 \times 10^{-9} \). The function \( y = f(x) \) is shown for each these formulations (Fig. 1).

**Relationship between E. coli O157:H7 occurrence in slaughtered cattle and vaccination**

The preceding discussion describes how human illnesses change with the number of colonized slaughter cattle, but our production function needs to relate human illnesses to use of cattle vaccine. To develop that relationship, we must describe how the number of colonized slaughter cattle will change as vaccine use increases.

We assume a simple linear relationship that describes how the number of colonized cattle \( (x) \) will decrease as the number of vaccinated cattle \( (z) \) in the population increases (Fig. 2). Because we assume that the status quo represents an unvaccinated population \( (z = 0) \), the line intercepts the \( y \)-axis at 3.2 million colonized cattle. The slope of the line is defined by the current prevalence of colonized cattle \( (x_0) \), the efficacy of the vaccine \( (e) \), and the required population coverage for herd immunity \( (h) \) (Equation 5). Efficacy is a common descriptor of the degree of immunity conferred on a vaccinated individual; it equals 1 if the vaccine ensures complete protection; otherwise, it is some value less than 1 (but greater than 0). The required population coverage for herd immunity describes the fraction of a population that theoretically must be rendered immune to halt transmission and eliminate the pathogen from the population (Anderson and May, 1990). It is not uncommon for vaccines to be evaluated for both efficacy and herd immunity, although research may be inconclusive or inconsistent across trials.

**Equation 5**

\[
x = 3.2 \text{ million} - \frac{e\pi}{h} z
\]

**Production function of fewer illnesses via cattle vaccination**

One can think of food safety as a production line where the product is human illness prevention. In economics, a pro-

---

**FIG. 1.** Alternative representations of \( y = f(x) \) are shown.

**FIG. 2.** Different assumed relationships between numbers of cattle colonized and vaccinated are shown. The thick dark line assumes that vaccine efficacy and required herd immunity are 100%. The broken gray line assumes that vaccine efficacy is 75% and required herd immunity is 100%. The thin gray line assumes that vaccine efficacy is 100% and required herd immunity is 75%.
production function describes the technical relationship that transforms inputs into outputs (e.g., Debertin, 1986). Human illnesses avoided can be thought of as an output. Similarly, interventions that prevent human illnesses (e.g., vaccinating cattle) can be thought of as an input to the food safety production process.

We define $Q$ as the number of human illnesses foregone as the result of $z$ vaccinated cattle [$Q = h(z)$]. Given the current unvaccinated status of slaughter cattle, $Q$ can be determined as the change in human illnesses that result as the number of colonized slaughter cattle is reduced:

$$Q = \Delta y = f(x_0) - f(x)$$

where $x_0$ is the current annual number of colonized slaughter cattle (i.e., 3.2 million head).

As described in the preceding section, $x$ is a linear function of $z$; thus, we can derive the production function $Q$ in terms of numbers of cattle vaccinated via substitution. Because there are two forms of $f(x)$, we have two production functions (Fig. 3);

$$Q = \left(\frac{\text{vaccine price}}{\text{vaccine price}}\right)z \quad \text{linear}$$

$$Q = b(3.2 \text{ million})^2 - b(3.2 \text{ million} - \left(\frac{\text{vaccine price}}{\text{vaccine price}}\right)z)^2 \quad \text{power}$$

Economic marginal analysis

In food safety, benefits are usually expressed in terms of value of illnesses foregone due to the implementation of a given mitigation. Similarly, costs are the monetary costs of planning, implementing, and maintaining the mitigation policy. In the case of marginal analysis in food safety mitigation, marginal costs are the additional costs that are incurred when one human illness is prevented. Similarly, marginal benefit is the value of one human illness prevented.

Marginal benefit of *E. coli* O157:H7 cattle vaccination.

Benefits are traditionally expressed as decreases in costs of illness due to a reduction either in the number of human illnesses or in the severity and associated treatments for those illnesses. Specific categories of costs of illness that have been typically quantified include lost work time, no physician visit/full recover, physician visit with full patient recovery, hospitalization with full patient recovery, hospitalization when patient develops chronic complications, and patient death and "value of life" considerations (Kuchler and Golan, 1999).

In this analysis, we define the marginal benefit of cattle vaccination as the value of one human *E. coli* O157:H7 illness prevented. The Economic Research Service (USDA) estimates the average expected cost of each *E. coli* O157:H7 illness at $6256 in 2007 dollars (ERS/USDA, 2008; Frenzen et al., 2005). This estimated cost includes consideration of the 78.5% of cases that never visit a physician and make a full recovery (with lost work and other costs totaling $29 per incident). Nevertheless, it also includes the 0.05% of cases that result in hospitalization and death (with an estimated economic cost of just under $7 million per incident). For simplicity of this illustrative analysis, we assume the marginal benefit is constant at $6256 per human illness avoided.

Marginal cost of *E. coli* O157:H7 cattle vaccination. If we know the cost per unit of vaccine ($v$), then the total annual cost of vaccination is $\text{TotalCost} = vz$. Using the production function, we can express total cost in terms of $Q$ and determine the marginal cost as the change in total cost for a change in output:

$$MC = \frac{\partial(\text{Total Cost})}{\partial Q}$$

Using the linear production function as an example, we can derive total cost and marginal cost as follows:

$$\text{Total Cost} = v \frac{hQ}{\text{vaccine price}}$$

$$MC = \frac{vh}{\text{vaccine price}}$$

A somewhat more complicated derivation of the MC function is needed for the power production function. It is easier to determine $Q$ using the production function for progressively larger numbers of vaccinates and simply calculate the difference in total cost divided by the difference in illnesses foregone in a spreadsheet.

The production, total cost, and marginal cost functions all depend on vaccine efficacy and herd immunity parameters. As previously explained, we assume that prevalence before introducing vaccination is 10% (i.e., $m_0 = 10$). For illustrative purposes, we examine three values (50%, 75%, and 100%) for both $\varepsilon$ and $h$.

By equating marginal cost and marginal benefit, we can determine the break-even cost per unit for vaccinating cattle given the linear production function (i.e., $v = (\text{Marginal Benefit})(\text{vaccine price}/h)$). However, marginal cost for the power production function is a function of output. In this case, we determine the optimal number of illnesses foregone (and vaccinations required) for alternative vaccination cost per unit assumptions by determining at what level of production marginal cost equals marginal benefit.

Results

Presented here is a case study that defines the break-even costs of a hypothetical *E. coli* O157:H7 cattle vaccine used to...
reduce the rate of *E. coli* O157:H7 illness in humans caused by consuming beef. We consider the results in terms of two different economic production functions (see Methods for details).

### A linear production function

For the linear production function, the break-even cost of vaccination ranges between $2.29 and $9.14 depending on vaccine efficacy and coverage required for herd immunity (Table 3). The smallest break-even cost of $2.29 per unit is associated with a vaccine efficacy of 50% and a required coverage for herd immunity of 100%. The largest break-even cost of $9.14 would occur if the vaccine were 100% efficacious and only 50% of the population needed to be vaccinated for complete elimination of the pathogen.

Break-even cost increases as vaccine efficacy increases, but it decreases as the required coverage for herd immunity increases. Improved vaccine efficacy will result in greater reductions in colonized cattle and, correspondingly, greater reductions in human illnesses, thereby supporting a higher cost per unit of vaccination. Reducing the required coverage for herd immunity implies that each unit of vaccination is more rapidly reducing the number of colonized cattle and human illnesses, so it similarly supports a higher cost per unit of vaccination.

When efficacy and the required coverage for herd immunity are equal, the break-even per unit cost of vaccination is always $4.57. In effect, the efficacy and herd immunity requirements cancel each other because these effects are influencing the break-even cost in opposing ways.

If decision makers were to consider the use of a real vaccine, the efficacy, required coverage for herd immunity, and cost per vaccinated animal would be known. As our analysis demonstrates, if vaccine efficacy was moderate (e.g., 75%) and required coverage for herd immunity was high (e.g., 100%), then the cost per vaccinated animal would need to be less than $3.43 to be considered cost effective. Thus, if the cost of the above vaccine was greater than $3.43 policy makers should look elsewhere until cost drops or efficacy improves. On the other hand, if the cost were less than $3.43, they should consider further analysis of policies supporting the use of such a vaccine.

#### Table 3. Break-Even Cost for a Vaccine Based on a Linear Production Function

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Required coverage for herd immunity</th>
<th>Break-even per unit vaccination cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>100%</td>
<td>$2.29</td>
</tr>
<tr>
<td>50%</td>
<td>75%</td>
<td>$3.05</td>
</tr>
<tr>
<td>75%</td>
<td>100%</td>
<td>$3.43</td>
</tr>
<tr>
<td>50%</td>
<td>50%</td>
<td>$4.57</td>
</tr>
<tr>
<td>75%</td>
<td>75%</td>
<td>$4.57</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td>$4.57</td>
</tr>
<tr>
<td>100%</td>
<td>75%</td>
<td>$6.10</td>
</tr>
<tr>
<td>75%</td>
<td>50%</td>
<td>$6.86</td>
</tr>
<tr>
<td>100%</td>
<td>50%</td>
<td>$9.14</td>
</tr>
</tbody>
</table>

Different combinations of vaccine efficacy and required coverage for herd immunity provide different break-even costs—ordered from smallest to largest.

#### The power production function

If a vaccine is cost effective when the linear relationship is considered, it will be cost effective for other plausible functions (see above and Methods). If, on the other hand, a vaccine is more costly than the relevant break-even cost in Table 3, we may need to conduct further analysis using the power production function. The power production function is a plausible description for how vaccination might influence human illnesses, particularly if evidence suggests that the distribution of doses in contaminated servings changes as the number of infected cattle changes (see Methods). In addition, the power production function may support alternative policy options by defining an optimal level of vaccine use that is less than what is required for complete herd immunity (i.e., vaccinating only a certain fraction of the total cattle may be a cost-effective policy).

If we assume that efficacy and necessary coverage for herd immunity are both 100%, then a graphical depiction of the marginal cost and marginal benefit intersection suggests—for arbitrary per unit vaccination costs of $3.00, $6.00, and $9.00—that the highest per unit vaccination cost will only be optimal to annually produce approximately 725 foregone human illnesses (Fig. 4). In other words, at a cost of $9.00 per vaccination unit, marginal cost and marginal benefit are equal when ~725 human illnesses are prevented. This level of human illnesses foregone occurs when roughly one-half million cattle intended for slaughter are vaccinated during 1 year. If more cattle were vaccinated at this cost, the additional costs of vaccinating would exceed the additional benefits returned in the form of human illnesses foregone.

If the per unit vaccination cost is assumed to be $3.00, then it will be optimal to prevent approximately 21,000 human illnesses each year (Fig. 4). This level of control will require vaccinating 22 million cattle intended for slaughter each year at a total cost of $66 million. The total benefits accrued as a result of foregoing 21,000 human illnesses is approximately $131 million (21,000 foregone cases × $6256 per case). Although the total benefits are nearly twice the total costs in this example, it should be noted that the benefit of foregoing the
last human case just equals the cost incurred to produce that foregone case. For example, another 2500 head of cattle would need to be vaccinated to produce one more foregone human case; the total cost of vaccinating those 2500 head would be $7500 while the additional benefit would remain $6256.

At a per unit vaccination cost of $6.00, it will be optimal to produce approximately 13,000 foregone human illnesses. This level of production is associated with vaccination of approximately 11 million cattle intended for slaughter. In comparison with the break-even cost ($4.57) for 100% efficacy and 100% required coverage for herd immunity in Table 3, this result suggests that a higher per unit cost of vaccination could be justified to accomplish a greater than 50% reduction in annual human illnesses if the power production function is assumed to be correct.

Using the power production function will generally support a higher per unit cost of vaccination regardless of vaccine efficacy or required coverage for herd immunity. For example, if $e = 50$ and $h = 100$, then a $4.00 per unit cost of vaccination will optimally produce about 5000 foregone illnesses using the power production function. In contrast, the linear production function determined a break-even cost of $2.29 for these parameter settings. Similarly, if $e = 100$ and $h = 50$, then a $13.00 per unit cost of vaccination will optimally produce about 12,000 foregone illnesses using the power production function compared to a break-even cost of $9.14 for complete herd immunity in the linear function (Table 3).

Discussion

A food safety policy analysis often begins with an inquiry about the effectiveness of an intervention to reduce human illness. If the intervention applies to live animals, then the initial question may be “what will be the effect of reducing infection among live animals on the occurrence of human illnesses?” The analysis presented here demonstrates a plausible method for answering this question, as well as examining the economic implications of that answer. The example used here is a hypothetical cattle vaccine that will reduce the occurrence of *E. coli* O157:H7—colonized cattle slaughtered each year in the United States. This analysis does not refer to any specific vaccine or other product that might reduce occurrence of *E. coli* O157:H7 among live cattle.

Using available data concerning the occurrence of *E. coli* O157:H7 among slaughtered cattle and human consumers, we derive two plausible relationships. After accounting for vaccine efficacy and required coverage for herd immunity, these relationships imply production functions for the number of human illnesses foregone given the input, number of cattle vaccinated. These production functions further imply economic break-even points or optimal levels of human illnesses prevented.

If a vaccine or other intervention is found to be cost effective using a linear or power function for $y = f(x)$, then that intervention would seem worthy of further public policy consideration. Our analysis shows that cost effectiveness of an intervention depends on the assumed relationship $y = f(x)$. With respect to *E. coli* O157:H7 in ground beef, a quantitative microbial risk assessment model suggested there was some correlation (i.e., a linear relationship) between cattle prevalence and probability of human illness per serving of ground beef, but that relationship was not further quantified (Ebel *et al.*, 2004). Our mathematical model suggests that a low-order power function could also describe the relationship between $y$ and $x$.

Endemic prevalence levels within an animal population influence vaccination policy. High endemic prevalence implies more return per animal vaccinated because each vaccine has a higher probability of becoming infected (or colonized). If prevalence is endemic at a low level, however, then all animals have a low probability of becoming infected and, to prevent any one animal from infection, many animals will need to be vaccinated. Based on evidence regarding colonized cattle, the prevalence of *E. coli* O157:H7 is moderately low (Rhoades *et al.*, 2008). This situation generally reduces the break-even cost of vaccination. Nevertheless, the prevalence of cattle that are contaminated on their hide surfaces may be substantially larger than the prevalence of colonized cattle (Rhoades *et al.*, 2008). If the hide-contamination prevalence was influenced by vaccination, then the economic break-even cost of vaccine might increase.

In this paper, we consider a preharvest intervention that reduces prevalence of infected cattle; however, we might also apply this model to an intervention that both reduces the prevalence of colonized cattle and the amount of organisms contained within those cattle that remain colonized. In such a case, the power production function is the appropriate relationship to assert. The linear production function is predicated on the assumption that changes in human illnesses depend only on changes in prevalence of colonized cattle (i.e., it is a prevalence-based model). Such an assumption provides a production function and analytic results that are mathematically simple. The power production function is less restrictive but more complicated. This function assumes that human illnesses change as a function of both the prevalence of infected cattle and the distribution of doses ultimately consumed (i.e., it is a prevalence and dose-dependent model). Although a precise functional relationship would require more analysis to derive, we expect that the power function of order 2 used in this paper is a reasonable upper-bound for the effect of a vaccine that substantively reduces animal-level prevalence and the doses ultimately consumed.

Other pathogens and animal products may represent extreme alternatives to the case presented here. For example, bovine spongiform encephalopathy (BSE) occurs at an extremely low frequency among cattle in many parts of the world, but the marginal benefit of preventing a human case could be very large. It is possible that the relationship between number of BSE-infected cattle slaughtered and human cases is directly proportional. The methods used for our example could be applied to this problem to determine the break-even cost of a vaccine that purports to prevent BSE cattle infections.

*Salmoneilla* in poultry represents a higher prevalence condition with human health costs similar to *E. coli* O157. It is expected that the break-even cost for a vaccine that prevented *Salmoneilla* colonization of poultry could be higher because of the higher prevalence of this microbial hazard under current (nonvaccinated) conditions.

To simplify the presentation, our hypothetical analysis of *E. coli* O157 in beef has ignored the effects of uncertainty. Nevertheless, substantial uncertainty attends our estimates of the actual annual numbers of human illnesses and colonized cattle slaughtered. Because the true current status regarding these values is uncertain, the alternative relationships
developed in our analysis (e.g., \( y = f(x) \) and \( Q = h(z) \)) are similarly uncertain. Because our methods are intended to provide a relatively simple preliminary analysis of a putative intervention such as vaccination, one approach to addressing uncertainty about \( x \) and \( y \) would be via sensitivity analysis. For the simple linear relationship, we know that a larger slope for \( y = ax \) will imply a smaller marginal cost for vaccination. To assess whether vaccination is cost effective under favorable conditions, we might choose a higher value of \( y \) (within its uncertainty range) while using a central value for \( x \); the marginal cost for these values would then be determined. As an alternative analysis, we would select a smaller value for \( x \) with a central value for \( y \) to determine another marginal cost. If both solutions implied the vaccine was cost effective, then more in-depth analysis could proceed. If the solutions were conflicting or both suggested the vaccine was not cost effective, then the need for further analysis could be re-assessed.

Our analysis demonstrates a method for screening pre-preparation interventions for their cost effectiveness. It is unlikely that we can ever empirically estimate a production function that relates the effect of an animal-level intervention on human illnesses. Relating animal occurrences to human illnesses is one reason for developing complicated farm-to-table quantitative risk assessment models. Nevertheless, the methods presented here support derivation of a production function using available data concerning occurrences of the pathogen among humans and animals. Given the production function, a particular intervention can be assessed for cost effectiveness using the marginal analysis techniques also demonstrated in this analysis. The ultimate policy decision concerning any intervention will necessarily be influenced by the effects of uncertainty, budgetary constraints, and other factors. More detailed analysis, beyond the methods developed here, would undoubtedly be needed before a final policy decision is made.

Disclosure Statement

No competing financial interests exist.

References


Address correspondence to:
Eric Ebel, Ph.D.
Risk Assessment and Residue Division
Office of Public Health Science
Food Safety Inspection Service
U.S. Department of Agriculture
2150 Centre Ave., Building D
Fort Collins, CO 80526
E-mail: eric.ebel@fsis.usda.gov