



**WHITE PAPER**

# **ALTERNATIVES TO COMMON PREVENTIVE USES OF ANTIBIOTICS FOR CATTLE, SWINE, AND CHICKENS**

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# Alternatives to Common Preventive Uses of Antibiotics for Cattle, Swine, and Chickens

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Over the past decades, a growing body of research confirms that the use of antibiotics in food animals is contributing to antibiotic resistance.<sup>1</sup> The more a particular antibiotic is used, the more chances bacteria have to evolve resistance mechanisms, and the less effective that drug may be in the future for use in people and animals alike. Low-level preventive uses may also have greater selective potential to allow resistance to occur than full-dose therapeutic uses.<sup>2</sup> Use of one antibiotic also can increase the spread of resistance genes to other, unrelated antibiotics.<sup>3</sup> Thus, it is critical that we engage in responsible stewardship of antibiotics by reserving them for use only when disease is present, and not as a regular preventive. In California, the passage of State Bill 27 (SB27) in October of 2015 marks a decision to address this issue, prohibiting regular use of antibiotics for disease prevention, and any use of antibiotics for growth promotion, starting in 2018. This paper focuses on common routine uses of antibiotics for disease prevention, and the alternatives to such use.

Nations such as Denmark, Sweden, and The Netherlands have been on the forefront of efforts to further reduce antibiotic use in food animals, and have begun to collect evidence that this has led to a decrease in resistant bacteria with modest to insignificant economic effects on producers or consumers.<sup>4</sup> In the United States, public sentiment and popular media coverage around the use of antibiotics for food animals has led to greater demand for, and production of, poultry and meat raised without antibiotics, including organic meat and poultry.<sup>5</sup> Understanding the experiences of producers and farmers from other countries, as well as non-antibiotic or organic producers here in the United States, can help guide efforts to decrease regular or ongoing preventive antibiotic use in cattle, swine, and chickens.

To better understand preventive antibiotic use in cattle, swine, and broiler chickens, as well as non-antibiotic alternatives

- we identified diseases in each species that are commonly treated with antibiotics. We searched the published literature, as well as veterinary texts and databases of approved drugs; we also consulted with veterinary experts in the academic community and who work directly with food animal producers for each of the species.
- we then identified non-antibiotic alternative products and management strategies that could help reduce preventive antibiotic use. Emerging therapies were discussed when peer-reviewed or independent studies existed showing evidence of their efficacy (including, but not limited to original studies based on field trials, systematic reviews,

and agricultural extension guidelines). Emerging therapies were also included when experts in the field who were interviewed recommended their inclusion. No specific endorsement of a product or brand is implied.

- we investigated and summarized the success of other countries in reducing their regular or routine use of antibiotics for disease prevention in cattle, swine, and chickens based on publications, articles, and first-hand sources.

**Table 1: Summary of alternatives to common preventive uses of antibiotics for cattle, swine and chickens**

Diseases		Alternative Practices
<b>All contagious diseases</b>		<ul style="list-style-type: none"> <li>• Biosecurity improvements,</li> <li>• Cleaning and hygiene,</li> <li>• Vaccination if available and effective</li> </ul>
<b>All diseases which result partially from stressful conditions or immune system challenges</b>		<ul style="list-style-type: none"> <li>• Husbandry changes providing animals with housing and living conditions more closely mimicking what they would encounter in a non-production setting</li> </ul>
<b>Calf scours</b>	neomycin, tetracyclines	<ul style="list-style-type: none"> <li>• Adequate colostrum intake</li> <li>• Antibodies, dried bovine plasma product</li> </ul>
<b>Bovine respiratory disease complex</b>	tetracyclines, florfenicol, tulathromycin	<ul style="list-style-type: none"> <li>• Preconditioning programs</li> <li>• Dietary manipulations and feed supplements</li> <li>• Probiotics and prebiotics</li> <li>• Remote early disease identification systems</li> <li>• Immunomodulatory medication</li> </ul>

<b>Liver abscesses in feedlot cattle</b>	tylosin, virginiamycin, tetracyclines	<ul style="list-style-type: none"> <li>• Higher levels of roughage and other feeding manipulations</li> <li>• Smaller groupings of cattle from single sources</li> </ul>
<b>Mastitis in dairy cattle</b>	penicillins, cephalosporins, novobiocin	<ul style="list-style-type: none"> <li>• Milking hygiene and practices</li> <li>• Teat sealants</li> <li>• Individualized approach to prevention</li> <li>• Screening of newly introduced cows and heifers for disease</li> </ul>
<b>Post-weaning diarrhea in piglets</b>	tetracyclines, tylosin, virginiamycin, bacitracin	<ul style="list-style-type: none"> <li>• Feed additives: organic acids, clay minerals</li> <li>• Later weaning age</li> </ul>
<b>Respiratory diseases in swine</b>	tetracyclines, ceftiofur, virginiamycin, bacitracin	<ul style="list-style-type: none"> <li>• Disease eradication</li> <li>• Age segregation</li> </ul>
<b>Intestinal disease in broiler chickens</b>	virginiamycin, bacitracin, lincomycin	<ul style="list-style-type: none"> <li>• Improved genetics and breeding</li> <li>• Lower protein, non-animal source diet</li> <li>• Probiotics, prebiotics</li> <li>• Organic acid supplementation in feed or water</li> <li>• Plant extract feed additives</li> </ul>

## 1. Common Disease Prevention Uses of Antibiotics in Cattle & Alternatives<sup>6</sup>

Challenges for cattle producers in both beef and dairy industries arise in prevention of common diseases which may have bacterial causes. Both beef and dairy calves are susceptible to diarrhea during their first few months of life. In adult cattle, the dairy industry uses antibiotics on a preventive basis for udder infections (also known as “mastitis”) in cows, while beef producers often seek to prevent respiratory disease complex and liver abscesses with antibiotics.

## 1.1 Diarrhea in calves (calf scours)

Diarrhea in newborn calves is known as scours, and is a common and important cause of death and economic loss. *E. coli* is the most common bacterial cause, although *Salmonella* and *Clostridium perfringens*, as well as various viruses and protozoa, can also be causes.<sup>7</sup>

Often, in an attempt to prevent scours, calves are fed a milk replacer containing antibiotics such as neomycin or oxytetracycline. However, routinely using antibiotics in this way to prevent scours raises the concern of selecting for bacteria resistant to these medically important antibiotics. Additionally, diarrhea in calves can have multiple contributing factors complicating identification of the cause. Without knowing the specific cause, or causes, adding antibiotics to milk replacer is likely to be ineffective in preventing diarrhea. For these reasons, the American Association of Bovine Practitioners no longer considers antibiotic additives to calf milk replacers to be best practice.<sup>8</sup>

### 1.1.2 Prevention of calf scours without the use of routine antibiotics

#### 1.1.2.1 Colostrum

Colostrum is the milk produced by the mother animal immediately after birth which is rich in factors that boost immune function and fight off infection. Consumption of adequate colostrum by a neonate to acquire passive immunity is a key factor in preventing calf scours, regardless of the cause. Experts recommend that calves consume at least 5 percent of their body weight in high-quality<sup>9</sup> colostrum within 6 hours of birth, and ideally within 2 hours of birth. Inexpensive testing that can be done stall-side can help calf operations ensure colostrum quality.<sup>10</sup>

#### 1.1.2.2 Vaccination, antibodies, and dried bovine plasma product

Another preventive measure against calf scours is vaccination of a pregnant cow against *E. coli* two weeks and again six days prior to calving, so that immunity from the cow will be passed to the fetal calf. Antibodies against *E. coli* are also commercially available and can be administered orally to calves immediately after birth if inadequate colostrum ingestion is suspected.<sup>11</sup>

An additional non-antibiotic option with promising results for preventing scours and improving weight gain is the addition of dried bovine plasma to milk replacer. Dried bovine plasma is a blood-derived by-product of slaughter which contains antibodies made by the adult cow. Calves are able to utilize those antibodies when they are fed orally and derive some immune benefit from them.<sup>12</sup>

### **1.1.2.3 Hygiene and disinfection**

Calf scours spreads when its various causative agents are shed and then transmitted by adult cows. Maintaining clean calving areas, as well as hygiene and disinfection protocols for workers, is important, as is the isolation of newborn calves from adult cows. An “all-in all-out” protocol where groups of calves are moved together helps prevent the spread of infective agents and allows for thorough cleaning of housing areas.<sup>13</sup>

## **1.2 Bovine Respiratory Disease Complex (Shipping Fever)**

Bovine Respiratory Disease Complex (BRDC), also known as “shipping fever,” is regarded as the most significant disease problem facing the U.S. beef industry.<sup>14,15</sup> Cattle being raised for beef are often transported over long distances and raised under densely concentrated conditions; the attendant stress is a major predisposing factor for BRDC. BRDC can lead to decreased rates of weight gain, as well as abortion losses in pregnant cows. Cattle with BRDC often have a fever, nasal discharge, develop pneumonia, and refuse to eat. Routine prophylactic antibiotic use is common, relying on antibiotics such as tetracyclines, florfenicol, and tulathromycin, all of which are ranked by the FDA as highly or critically important.

While housing and transport are predisposing stresses, BRDC has multiple infectious causes, including interactions between various bacteria and viruses. *Mannheimia haemolytica* is the bacteria most commonly isolated in BRDC, and *Pasteurella multocida* and *Histophilus somni* can also be implicated.<sup>16,17</sup> Because multiple factors can cause or contribute to BRDC, there is no single method to prevent its development. As with many diseases occurring in stressed animals, a combination of measures to lower stress and boost immunity is the best means to prevent illness in the first place.

### **1.2.1 Prevention of Bovine Respiratory Disease Complex without the use of routine antibiotics**

#### **1.2.1.1 Vaccination**

An analysis combining results from 15 different studies looked at the efficacy of vaccines against the three bacteria that cause BRDC. The analysis found benefits for vaccinating feedlot cattle against *M. haemolytica* and *P. multocida*, but not for vaccination against *H. somni*.<sup>18</sup> Vaccination against the viral components of BRDC (Bovine Viral Diarrhea Virus, and Bovine Infectious Viral Rhinotracheitis, caused by Bovine Herpesvirus-1) is also effective at preventing BRDC, and therefore is standard practice as part of a comprehensive disease prevention program.<sup>19</sup> Additionally, implementing a strong vaccination program for cows during pregnancy and prior to birth can help assure passive transfer of immunity via colostrum.<sup>20</sup>

### *1.2.2.2 Biosecurity<sup>21</sup> and hygiene*

Standard measures to control contagious disease are important in reducing the incidence of BRDC, and should be made universal practice. There should be clear expectations and protocols for disease prevention as cattle arrive at sale or feedlot settings; experts recommend that these include

- Prompt isolation of sick individuals,
- Cleaning and disinfection of feed and water apparatus and transport vehicles,
- Measures to ensure adequate ventilation, and reduce airborne dust particles which have been shown to impair normal respiratory tract defense mechanisms.<sup>22</sup>

### *1.2.2.3 Preconditioning programs*

Preconditioning refers to preparatory measures that are taken for approximately a month of time following weaning of calves to ensure successful weight gain in a feedlot. A preconditioning program can be implemented to ensure calves have been vaccinated, dewormed, and accustomed to the types of food and water troughs they will encounter during shipping. Any surgical procedures to be performed on the calves, such as castration or dehorning, should be performed with plenty of time for healing prior to transport.<sup>23</sup> Calves are often sold and transported immediately following weaning. However, industry experts such as Purdue University's extension service and Canada's Beef Cattle Research Council recommend waiting an additional month while preconditioning calves to aid cattle health and help avert the need for preventive antibiotics when undergoing the stresses of transport.<sup>24,25</sup>

### *1.2.2.4 Dietary manipulations and feed supplements*

Modifications to feeding can also boost immunity, and lower incidence of BRDC. As they arrive at a feedlot, calves must become used to a concentrated, high-energy diet in order to gain weight rapidly; however, initial diets with the highest percentages of grain and lowest percentages of hay or roughage may increase the likelihood of BRDC.<sup>26</sup> Many studies have looked at the role of various supplements and minerals on the rate of BRDC. Because the severity and incidence of a disease is subjective, those studies often rely on "average daily weight gain" as a measure of health. Review articles concluded a benefit to average daily weight gain in beef cattle when their feed was supplemented with Vitamin E and with zinc. For other vitamin and mineral supplements, definitive conclusions remain elusive.<sup>27</sup> However, it is generally held true that adequate feed intake overall is associated with lower rates of disease, so making sure calves can access feed bunks and learn to use water troughs should help achieve good nutritional status and improve immune function.<sup>28</sup>

#### **1.2.2.5 Probiotics and prebiotics**

The use of probiotics (also known as direct-fed microbials) and prebiotics to improve weight gain and decrease illness among newly-received beef calves is an area deserving more investigation. Probiotics are living bacterial organisms. Prebiotics, by contrast, are building blocks of metabolism which can help promote the growth of gut bacteria. Commercial probiotic products are available and recommended by such groups as the Bovine Alliance on Management and Nutrition, a coalition of participants from the following member organizations: the American Association of Bovine Practitioners, the American Dairy Science Association, the American Feed Industry Association, and the United States Department of Agriculture.<sup>29</sup> They include such bacteria as *Lactobacillus acidophilus* and *Bifidobacterium*, which consumers are familiar with as the “live, active” cultures in yogurt. Probiotics alter intestinal flora in a positive manner and compete with unwanted disease-causing bacteria.<sup>30</sup> While there is little published evidence of the efficacy of these strategies in cattle, there is clear published evidence that probiotics and prebiotics are useful in broiler chickens (discussed below). It may be that because cattle are larger, longer-lived, and more valuable animals compared to chickens, studies proving statistical significance are more difficult to design.

#### **1.2.2.6 Remote early disease identification systems**

Advanced monitoring systems show some promise in helping to avoid administering antibiotics to entire herds when only some animals are ill. One kind of remote early disease identification system (REDI) works by placing an electronic ID tag on each calf, and then remotely monitoring the animal’s motion, time spent in groups, and positioning. A different system works by using a thermal camera mounted near feed or water stations. Information from either system, using an algorithm, can predict whether an individual animal is likely to be suffering from BRDC. Remote systems require less intensive staffing, and have proven as accurate as a trained observer in predictions of illness.<sup>31</sup> Isolating and treating sick individuals more promptly can reduce or avoid antibiotic use in the herd overall. In one test, herds of calves monitored with a REDI and treated only when sick were found to have similar disease rates compared to herds where *all* newly arrived calves were given antibiotics presumptively.<sup>32</sup>

#### **1.2.2.7 Immunomodulatory medication**

A newly-available, non-antibiotic medication works by stimulating the immune system to respond rapidly to *M. haemolytica*.<sup>33</sup> Cattle injected with this medication, when compared to a control group given preventive antibiotics, had no significant difference in terms of their average daily weight gain or incidence of BRDC infections.<sup>34</sup>



## 1.3 Liver abscesses

At slaughter, abscesses are commonly found in livers of both dairy and beef cattle. Abscesses are pockets of pus and bacteria walled off from surrounding tissue. Cattle with liver abscesses often have no outward signs of disease, but gain weight more slowly, and at slaughter parts of the carcass including the liver and surrounding organs may be condemned.

The bacteria most commonly identified from liver abscesses is *Fusobacterium necrophorum*, which is present as part of the normal bacterial flora in the ruminant stomachs of cattle. In intensive feeding operations characteristic of many beef and dairy production systems, cattle are fed a diet consisting of more calories and higher proportions of grain than they would normally consume as grazers on pasture. The sugars present in grain ferment during the cow's digestive process, leading to production of lactic acid which then contributes to small pockets of infection on the rumen wall. Those infection-causing bacteria then move through the bloodstream and cause larger pockets of infection or abscesses in the liver. In beef operations, medically important antibiotics (tylosin, virginiamycin, oxytetracycline or chlortetracycline) are often added to feed in an attempt to prevent liver abscesses. Of these, tylosin is most commonly used<sup>35</sup> and as a macrolide antibiotic, it is in a class considered critically important for human use.<sup>36</sup>

### 1.3.1 Prevention of liver abscesses without the use of routine antibiotics

#### 1.3.1.1 Use of higher levels of roughage in diet and other feeding manipulations

Prevention of liver abscesses focuses on avoiding overproduction of lactic acid by providing a diet higher in roughage (hay) and giving cattle more time to adjust to high-calorie, grain-rich feed.<sup>37</sup> An increase in the number of feedings per day, or allowing *ad lib* feeding for newly arrived cattle, can also increase mastication or chewing time. This in turn increases the natural antacid effect of saliva, which can help neutralize lactic acid production during metabolism. Another important factor is avoidance of foreign objects in food, which can injure the rumen wall and result in the formation of more abscesses.<sup>38</sup>

#### 1.3.1.2 Vaccination

Vaccination of cattle against *Fusobacterium* when they enter the feedlot may reduce abscess incidence and severity. Interestingly, the protective effect of vaccination was seen in groups of cattle who were given unlimited access to hay during early growth, and was not statistically significant in cattle fed a grain ration only, although both groups of cattle were fed grain during the final or "finishing" period of growth prior to slaughter.<sup>39</sup> In this case, the positive effects of

diet manipulation plus vaccination are additive in reducing the need for antibiotic use on a preventive basis.

### ***1.3.1.3 Consider smaller groupings and single sources of cattle***

Conventional wisdom has been that preventive antibiotic treatment improves profitability by increasing weight gain and decreasing liver abscess incidence and severity.<sup>40</sup> New research shows that in some low-risk cattle, at least, there is no benefit to routine feeding of antibiotics. Specifically, a recent study showed that in cattle housed in small pens for finishing who came from a single source, the feeding of either tylan or a tetracycline antibiotic did not lead to any improvement in growth or decrease in abscess occurrence, compared to cattle in identical conditions that were not fed antibiotics.<sup>41</sup>

## **1.4 Mastitis in dairy cattle**

Bacterial mastitis, or inflammation most often caused by infection of the udder, is the most common reason for routine preventive antibiotic use in dairy cattle, and remains the largest cause of economic loss within the dairy industry. It is estimated that 80% of all antibiotics used in dairy cattle are for prevention or treatment of mastitis.<sup>42</sup>

Non-lactating, or “dry” cows are commonly given antibiotics to treat existing subclinical infections and to prevent against new infections caused by environmental pathogens. Subclinically infected cows do not always show symptoms of mastitis such as swollen, painful udders and abnormal-appearing milk. However, a cow with subclinical disease can still have decreased milk production. Dry cow therapy (DCT) consists of infusing antibiotics directly into the udder at the time that milking ceases, approximately two months before calving. Following calving, milk production starts again and is known as the “wet” period. The most common antibiotics used for DCT are penicillins, cephalosporins, and novobiocin.<sup>43</sup>

Common bacterial causes of mastitis are *Staphylococcus aureus*, *E. coli* and environmental *Streptococci*, with *Mycoplasma*, coagulase-negative *Staphylococci*, and various other bacteria playing a lesser role. Contagious mastitis spreads from one cow to another, either via direct contact or indirectly via contaminated milking equipment or workers. While mastitis has infectious causes, environmental conditions can influence whether the bacteria which are present will cause disease. Environmental factors contributing to mastitis consist of poor milking conditions and a generally unclean or inappropriate housing environment. To prevent mastitis without preventive antibiotic use requires improving environmental conditions as well as decreasing contagious risks.<sup>44</sup>

## 1.4.1 Prevention of mastitis without the use of routine antibiotics

### 1.4.1.1 Environmental management, sanitation, and milking hygiene

Good sanitation and hygiene during the dry cow period and initiation of milking, as well as proper management of the calving area, are crucial to minimizing infections, and have been associated with a lower incidence of clinical mastitis.<sup>45</sup>

Other measures to reduce mastitis include the following:

- Provide **appropriate bedding** and surfaces for cows – an inorganic bedding such as sand is preferred as it supports less bacterial growth than straw, sawdust or compost;
- Ensure milking **equipment functions properly** (i.e. provides an appropriate vacuum and pulsation) to avoid teat trauma;
- Prepare heifers by **pre-milking stimulation**- In heifers, prior to calving for the first time, preparation of the udder by milking either two or three times daily for two weeks prior to expected calving showed up to a 55% reduction in development of mastitis.<sup>46</sup>
- Practice **good teat hygiene**, including cleaning and drying teat ends thoroughly for each cow during milking, and using individual towels for each animal.
- Use a **post-milking teat dip** with an iodophor disinfectant which has been shown to provide better coverage than a spray.<sup>47</sup>

### 1.4.1.2 Teat sealants

A known alternative to treatment of dry cows with antibiotics (DCT) is the use of teat sealants. Teat sealants mimic the natural keratin plug that forms in the teat canal at the end of the lactation period, and prevent environmental bacteria from ascending into the udder and causing mastitis. In a meta-analysis of 12 studies, the use of internal teat sealants reduced the risk of new intramammary infections by 25% whether or not antibiotics were infused concurrently, and resulted in a 73% reduction in mastitis risk compared to non-teat-sealed cows.<sup>48</sup> One study further suggests that teat sealants may perform better on their own than when combined with antibiotics. The study showed a 12 times higher rate of clinical *E. coli* mastitis developing in the next lactation cycle when uninfected cows were treated with an antibiotic product and sealant versus with a teat sealant alone. The article theorized that antibiotic treatment in uninfected cows can actually cause an increased risk of mastitis by removing beneficial normal bacteria.<sup>49</sup> Teat sealant use instead of antibiotic DCT has become widespread in European Union countries and is even mandated by some milk buyers as a required practice for their farmers.<sup>50</sup>

### **1.4.1.3 Vaccination**

A vaccine -- based on J5 mutant *E. coli*-- is now available to help reduce the severity of mastitis caused by coliform bacteria. Vaccination should include multiple doses during the dry period and in early lactation to reduce the risk of clinical mastitis developing during lactation.<sup>51</sup> Newer research into a promising vaccine which contains *E. coli* as well as *Staphylococci* showed that vaccinated cows were less likely to experience clinical mastitis and produced more milk than non-vaccinated herdmates.<sup>52</sup>

### **1.4.1.4 Individualized approach to mastitis prevention**

Different dairies have different risk factors and management practices that require an individualized approach to preventing mastitis. An individualized approach involves working closely with a veterinarian or consultant to analyze patterns of mastitis within the herd, and identify key areas for improvement. In the United Kingdom, focus on tailoring prevention protocols to individual dairies resulted in a 22% reduction in cows affected with clinical mastitis.<sup>53</sup> The tailored approach became a core component of a national program to control mastitis in the UK,<sup>54</sup> adopted by at least 1100 dairies since its launch in 2009.<sup>55</sup>

### **1.4.1.5 Assure newly-acquired cattle are disease-free**

To avoid introducing mastitis-causing bacteria, new heifers and cows should be purchased from a trusted and well-managed herd with good record-keeping and evidence of a mastitis control program. If bought from an outside source, experts recommend that cows should be tested for contagious causes of mastitis, be subject to an initial quarantine period, and should be milked last until proven free of disease.<sup>56</sup> Some larger herds even maintain closed operations, meaning the heifers which will become milking cows are bred on-site.

## **1.4.2 Case study- organic dairy production in the US**

In the US, organic standards dictate that no antibiotics can ever be used for a cow whose milk will be sold as organic.<sup>57</sup> An American veterinarian who works for an organic dairy cooperative is planning to help 400 new farms make the transition from conventional to organic milk production over the next three years. As part of the transition away from the use of antibiotics, the importance of good husbandry and milking technique is stressed to the producers. From experience, organic producers have learned the importance of checking for any early signs of mastitis prior to the end of the milking period. If a cow begins showing early signs of mastitis, milking techniques can be changed to prevent full-blown mastitis from developing. Affected glands can be "stripped," which means completely emptied of milk more frequently, to help prevent the need for antibiotic treatment. Also, as the end of the milking or wet period approaches, the veterinarian recommends tapering down the amount of milk being obtained. A

cow that ends her milking period with gradually diminishing milk production, rather than having milking stop abruptly while she is still producing high yields, will be less likely to develop mastitis. A gradual decrease in the amount of feed given also helps lower milk yields slowly.<sup>58,59</sup>

Organic producers stress the importance of paying attention to preventive care and husbandry during all times of the cow's milking cycle. While it may be tempting to treat the dry cow period as a time when cows are low-maintenance, they find it is equally important to be vigilant about husbandry and hygiene during that time. For example, during the dry period just prior to calving, it is important to watch for milk production beginning as cows may start leaking milk and their bedding must be kept clean and dry to prevent infection.<sup>60</sup>

Veterinarians for organic producers also report success with probiotic treatment for calf scours. Since antibiotics are prohibited, they recommend focusing on providing good bacteria for the gut from sources such as yogurt, rather than turning to preventive antibiotics to ward off disease-causing bacteria.<sup>61</sup>

## **2. Common Disease Prevention Uses of Antibiotics in Swine & Alternatives<sup>62</sup>**

Giving antibiotics routinely to pigs is widespread practice to prevent diarrhea in piglets just after weaning and respiratory disease in growing pigs. An estimated 70-80% of piglets and 60-70% of growing pigs receive antibiotics.<sup>63</sup> In the most recent US data from voluntary surveys,<sup>64</sup> over 80% of farmers reported having used antibiotics for groups of pigs for disease prevention or control within the previous six months. The most commonly used antibiotics by respondents are the tetracyclines, tylosin, virginiamycin, bacitracin, and ceftiofur.<sup>65</sup>

Since there is considerable overlap in methods to decrease preventive antibiotic use for diarrhea versus for respiratory disease, we first discuss general approaches to both. Following that, we discuss each disease in turn followed by specific antibiotic alternatives that are most relevant to it.

### **2.1 General ways to reduce routine antibiotic use in swine**

#### **2.1.1 Biosecurity**

Biosecurity is critical to decreasing use of preventive antibiotics in swine. Put simply, biosecurity entails understanding and preventing conditions that give rise to the transmission of infectious

disease. Any item, person, or animal that enters a farm – including the pig itself – can bring with it disease-causing microbes. Possible vectors of disease brought to the farm can include birds, insects, other non-swine animals such as dogs, cats or rodents, as well as farm personnel and vehicles. Biosecurity is therefore an essential piece of the puzzle in reducing swine disease while also reducing the routine use of antibiotics.<sup>66</sup>

### **2.1.2 Hygiene and cleaning**

Hygiene –the cleaning and disinfection of pig housing-- is also paramount to keeping animals healthy, and reducing routine use of antibiotics. In countries such as Denmark where there is a strong national antibiotic-reduction program, farmers are counseled to follow key recommendations as published in the “Guidelines for Good Antibiotic Practice.”<sup>67</sup> The Danish guidelines, E.U. Commission guidelines,<sup>68</sup> and discussions with industry veterinarians,<sup>69</sup> point to the following practices:

- Clean areas housing the youngest pigs first, then move to those housing more mature pigs. Clean pens for sick pigs last.
- Allow floors to air dry after cleaning and disinfecting, or use an air dryer. Discourage use of disinfectant in pools of standing water, which is ineffective.
- Make boots available outside each barn or facility, so staff can change footwear and avoid contaminating each new area to be cleaned.
- Move groups of pigs together to entirely empty a pen, so it can be cleaned thoroughly, and so new animals are not exposed. This “all-in, all-out” mode of production helps prevent spread of infectious disease between groups of pigs.
- Never move runts -- pigs whose growth lags behind others in their age group -- into groups of younger pigs. Keep them with their age group. As discussed below, age segregation is an especially important tool for prevention of respiratory disease.
- Pay special attention to ventilation systems when cleaning. Most respiratory disease is transmitted through the air by coughing and nasal discharge of sick pigs.
- Clean feed apparatus thoroughly, and maintain it on a schedule. Oversupply of feed can result in spillage of feed and pigs eating from the floor which is unsanitary, or overeating which can cause intestinal problems. Undersupply or poor ordering and delivery timetables can result in periods without food which is stressful for pigs and can lower immune function.

## **2.2 Post-weaning diarrhea**

Immediately after weaning, piglets’ gastrointestinal tracts must adjust to a non-milk diet. During this period, piglets are vulnerable because a mature, well-functioning gut is crucial to good immunity. The incidence of diarrhea, or scours, is high, and can result in significant losses through dehydration, poor growth, or even death. The most common bacterial cause of scours

in newly-weaned pigs is *E. coli*, and co-infection with viruses such as rotavirus makes diarrhea more severe. *Lawsonia intracellularis* (the causative agent of porcine proliferative enteritis), *Salmonella*, and *Brachyspira* are other possible causes.<sup>70</sup>

## 2.2.1 Protecting against post-weaning diarrhea without the routine use of antibiotics

### 2.2.1.1 Stress Reduction

In newly-weaned piglets, reduction of physiological stress is especially important. Difficulty regulating body temperature can be a source of stress, so an extra heat source should be provided if environmental conditions require it. Experts recommend adding straw to housing and taking measures to reduce drafts since young piglets are susceptible to hypothermia.<sup>71</sup>

Giving piglets time to adjust to their post-nursing diet can also help decrease physiological stress. Specifically, lowering the protein content in their feed for the first few days can be beneficial, as their intestines transition away from a milk diet.<sup>72</sup> From a mechanical perspective, even the smallest pigs should be able to reach feed and water, as inability to do so will add to stress.

### 2.2.1.2 Feed additives<sup>73</sup>

- **Organic acids** – such as citric, lactic, and formic acids– added to feed as a supplement in the immediate post-weaning period can be beneficial. Digestion of solid feed requires a more acidic gut environment than digestion of milk, and the production of digestive stomach acids requires a mature gastrointestinal tract. Because piglets are being fed solid feed while their gastrointestinal tracts are still maturing, supplementing the feed with acid initially can help improve digestion, and can mean less diarrhea. Additionally, the feeding of organic acids may also directly suppress bacterial growth in the gut; piglets whose feed was supplemented with organic acids had significantly lower numbers of *Salmonella* and *E. coli* in their stomachs, and shed fewer bacteria in their feces.<sup>74</sup>
- **Clay minerals** can also be added to a pig's diet and have the ability to bind and absorb diarrhea-inducing toxins produced by *E. coli* bacteria, without negatively impacting the animals' growth or digestion. Many studies document that giving dietary clay to pigs can improve growth and lower rates of post-weaning diarrhea.<sup>75</sup>

### 2.2.2.2 Later Weaning Age

Early weaning has a negative effect on immunity, and predisposes pigs to post-weaning diarrhea.<sup>76</sup> Simply keeping piglets with sows longer has also been shown to improve overall lifetime weight gain. One study showed that a weaning age of 21.5 days resulted in improvement in weight at the time of slaughter compared with earlier weaning at 12 days of age.<sup>77</sup>

### 2.2.2.3 Vaccines

Vaccinating sows can prevent some forms of *E. coli* diarrhea in their piglets by improving the transfer of antibodies created by the sow to the piglet. Piglets can also be vaccinated directly against *Lawsonia* either injectably or as an oral vaccine in drinking water. Compared to injecting all the pigs in a herd, oral administration of vaccines can reduce stress on pigs, while also saving on labor costs.<sup>78</sup>

## 2.3 Respiratory disease

Respiratory disease in swine is a complex syndrome in which environmental factors interact with infectious agents to result in illness. Many pigs are carriers of respiratory bacteria such as *Mycoplasma*, but do not show illness. Pigs are more likely to become sick when multiple species of bacteria, or bacteria plus viruses, are present, as some of these pathogens have a positive feedback effect on each other. For example, while infection with *Bordetella* may only cause mild cold-like symptoms which resolve on their own, when both *Bordetella* and *Pasteurella* bacteria are present, an infected pig may become sick with atrophic rhinitis. Atrophic rhinitis is marked by changes within the nasal tissue and sinuses which can become severe enough to cause respiratory distress, and which prevent pigs from gaining weight.<sup>79</sup>

Other common respiratory diseases in swine include enzootic pneumonia and pleuropneumonia. Enzootic pneumonia can be mild when caused by *Mycoplasma* alone; interaction and secondary infection with *Pasteurella*, however, results in more severe disease. Pigs suffering from enzootic pneumonia cough and gain weight poorly. Pleuropneumonia is caused primarily by *Actinobacillus pleuropneumoniae*; it is characterized by fevers, nasal discharge, and sometimes death due to respiratory distress.<sup>80</sup>

Finally, an additional disease which is spread through the respiratory tract but which can cause high fevers and lameness is known as Glässers disease. The causative agent is a bacterium called *Haemophilus suis*. Many pigs are carriers of *Haemophilus*, but if piglets have not received good protective immunity from the sow's colostrum or if the herd is newly exposed by introduction of carrier individuals, then active disease can develop.<sup>81</sup>



## 2.3.1 Protecting against respiratory disease in swine without the routine use of antibiotics

### 2.3.1.1 Disease eradication

Positive carrier status of a swine herd for *Mycoplasma* bacteria appears to be a key factor accounting for antibiotic use in those herds. It is possible to make a plan to eradicate *Mycoplasma* from the entire herd. Permanently removing the pathogen from the herd can help decrease long-term use of antibiotics, as well as carry economic benefits. An eradication program involves introducing no new animals to the herd for at least 8 months, vaccinating the entire breeding herd, and the administration of antibiotics to piglets to remove any carriers of *Mycoplasma*. This involves using antibiotics, which may seem counterproductive, but carries with it the possibility of the longer-term benefit of reduced administration of antibiotics to a far greater number of pigs.<sup>82</sup>

### 2.3.1.2 Prevention of mixing of different age groups

Weaning and then maintaining piglets in age-segregated groups has been shown to be effective in preventing transmission of many of the respiratory pathogens from adult carriers to newborns.<sup>83</sup> During transportation from one facility to another, or if new breeding pigs are being acquired, it is especially important to limit mixing of age groups of pigs. The stress of transportation and exposure to pigs from different facilities can be concurrent risk factors for development of disease, and must be kept in mind when attempting to limit the use of preventive antibiotics.

### 2.3.1.3 Vaccines

Vaccines are available against some of the bacteria which cause respiratory disease in swine. An *Actinobacillus* vaccine has been shown to be effective against pleuropneumonia<sup>84,85</sup> and vaccination against *Pasteurella* prevents pigs from developing atrophic rhinitis.<sup>86,87</sup> Vaccination against *Mycoplasma* can also reduce the severity of respiratory disease, especially in the case of co-infection with viral respiratory disease.<sup>88</sup> In a comprehensive vaccine program, viral diseases such as porcine circovirus, swine influenza virus, and porcine reproductive and respiratory syndrome virus should also be considered as candidates for vaccination since co-infection with viruses is an important component of respiratory disease in pigs.<sup>89</sup> University cooperative extension services can provide appropriate recommendations for a vaccine schedule.<sup>90</sup> In all cases where a vaccine program is being considered or initiated, it is important to work closely with a veterinarian to positively identify which diseases are present in the herd. Samples must be collected and submitted to a lab, and sometimes affected pigs should be slaughtered to obtain the best samples.

## 2.4 Case Study- Denmark

In countries where routine use of antibiotics has been banned, a wealth of information regarding best practices to minimize disease and maximize production without antibiotics has become available. Danish farmers have reduced antimicrobial use in animals by 44% between 1994, when the phase-out of routine uses was initiated, and 2014, while increasing pork production by 15%.<sup>91</sup> To achieve this, Denmark focused primarily on giving farmers and veterinarians the resources they needed to encourage good antibiotic stewardship, including step-by-step how-to guidelines written for producers, research into best practices surrounding antibiotic reduction, and monitoring on a nationwide scale. Danish experts produced a Manual on Good Antibiotic Practice,<sup>92</sup> and established the Danish Pig Research Centre.<sup>93</sup> The Danish Manual on Good Antibiotic Practice emphasizes husbandry and biosecurity principles like those discussed above. Denmark also instituted a national monitoring system which produces annual reports on antibiotic use and resistant bacteria called DANMAP.<sup>94</sup>

Finally, the Danish Pig Research Centre focuses on providing cutting-edge information in the following areas:

- *enhanced biosecurity to prevent and control the introduction, spread as well as the severity of infectious disease on and between farms,*
- *enhanced natural disease resistance by selective breeding, development of feed which causes less enteric infections (e.g. easily digestible feed),*
- *enhanced efficiency to identify individual sick animals for treatment to replace preventive herd treatment,*
- *and vaccination of animals to prevent disease<sup>95</sup>*

As research findings are collected and published, the information is used to guide producers' decisions on when antibiotic use is appropriate, and as a way to make sure that husbandry methods are used as a first line of defense against disease, rather than preventive medication.

For instance, a farmer near Copenhagen who produces around 25,000 piglets per year, which he sells to other farmers for raising to market weight, discussed biosecurity and avoidance of any possible contamination of his farm as a priority. His pigs are certified as specific pathogen free (SPF) which means they do not carry certain diseases such as *Mycoplasma* or atrophic rhinitis, and therefore can be sold at a higher price to other farms. In the interest of maintaining this certification, he requires all visitors including veterinarians and advisors to have a 12 hour quarantine period and to wear complete protective gear. He also takes special precautions surrounding transport of pigs, and will not allow any outside vehicles onto his farm, requiring them to park at a distance from his barns. He transports the pigs only in his own SPF trailer, and disinfects it afterwards. Finally, as part of a general program of stress reduction and comfort for his breeding sows, which contributes to overall health, he provides a shower system for cooling,

and has the pigs fitted with electronic tags which interface with his feeder to dispense the proper food for each pig.<sup>96</sup>

### 2.5 Case study- Sweden

In Sweden, a national strategy for the monitoring of antibiotic use in both humans and animals has been put into place. The strategy takes a three-fold approach to antimicrobial reduction based on surveillance of use, prevention of disease by good management practices, and basing all antibiotic use on correct medical diagnoses.<sup>97</sup>

Attention to husbandry measures similar to those found to be successful in Denmark has been key to reduction of preventive antibiotic usage for Swedish pork producers. A Swedish veterinarian discussed his focus “on good management strategies, vaccination and looking at the natural behaviors of the pigs and especially the sows in order to get strong piglets that are well prepared to deal with infections and stressful events.”<sup>98</sup>

## 3. Common disease prevention uses of antibiotics in broiler chickens and alternatives<sup>99</sup>

Chicken is Americans’ number one meat consumed in pounds per capita,<sup>100</sup> and is seen as an affordable and healthy protein source. As producers meet growing demands for broiler chicken meat, preventive antibiotic use has become common in the industry. Preventive uses of antibiotics in broiler chickens are related to intestinal disease prevention in growing birds, and injection of antibiotics directly into the eggs of chicks prior to hatching to prevent bacterial contamination.

### 3.1 Intestinal disease in broiler chickens

Routine antibiotic use in growing broiler chickens centers on prevention of intestinal disease. Intestinal disease is a major economic factor in the poultry industry, accounting for annual losses estimated at more than 2 billion dollars worldwide.<sup>101</sup>

Preventive use of antibiotics is aimed at necrotic enteritis, caused by *Clostridium perfringens*, usually in the presence of other complicating factors. Clostridial bacteria are ubiquitous in the environment, and can exist at low levels in the intestines of poultry, as well as other species such as humans, without causing disease. However, when other predisposing factors occur, such as environmental stress or concurrent infection with *Salmonella* or coccidia (a single-celled

parasitic organism), *Clostridium* proliferates and begins to produce toxins. Those toxins damage the cells lining the intestinal tract of the chicken, often resulting in a sudden increase in mortality within a flock. Subclinical infections can also occur in which birds do not show active disease, but have poor weight gain due to low-level damage to the digestive tract.<sup>102,103</sup> Lethargy in birds, ruffled feathers, and diarrhea may also be observed. Antibiotics that are commonly used preventively include virginiamycin, bacitracin, and lincomycin.<sup>104,105</sup> However, with growing concerns around routine antibiotic using in poultry, there is heightened interest in non-antibiotic methods for preventing necrotic enteritis.

### 3.1.1 Protecting against intestinal disease in broilers without the use of routine antibiotics <sup>g</sup>

#### 3.1.1.1 Environmental conditions, hygiene, and biosecurity

Major U.S. poultry producers note the importance of optimizing environmental conditions to prevent intestinal disease in broiler chickens. As in other species, experts cite biosecurity and hygiene measures as critically important to maintaining healthy flocks. Disinfectant procedures should be adhered to, and expectations for workers and visitors to maintain biosecure premises must be clear. All-in, all-out protocols for moving groups of birds and cleaning housing should also be followed.<sup>106</sup> Additionally, any cleaning or husbandry measures aimed at reduction of coccidia are also helpful in prevention of necrotic enteritis, as co-infection is a major risk factor for development of intestinal disease.<sup>107</sup>

A recent panel of industry experts discussed the following factors which have helped their operations transition to lower or no preventive antibiotic use:

- Improved **ventilation** and **decreased bird density**;<sup>108</sup>
- **Moisture control** by managing watering equipment to prevent leaking or wet spots which can help reduce presence and growth of *Salmonella* and *E. coli*;<sup>109</sup> and
- **Effective litter** management between flocks which can include in-house composting, litter acidifiers, and time to rest between flocks.<sup>110</sup>

#### 3.1.1.2 Improved genetics and breeding

Some traits which may cause increased susceptibility to infections are influenced by genetics. Through breeding, producers have successfully reduced the incidence of leg disorders, and susceptibility to heart and lung problems in broilers; success may be achievable with respect to incidence of other diseases.<sup>111</sup> Newer research into the molecular basis of disease susceptibility and immune function may be able to produce chickens with innate resistance to some bacteria, and is an area of active study.<sup>112</sup>

### 3.1.1.3 Lower protein or non-animal source diet

Higher dietary protein levels, as well as animal sources of protein in the diet, may result in an increased risk of necrotic enteritis. In a study in which one group of chickens was fed a soy-based protein, they were found to have significantly fewer *Clostridium* in their intestines compared with a group fed animal-source protein. The same study looked at protein levels overall and found that a higher protein level, regardless of source, was also correlated with more *Clostridium*.<sup>113</sup> A combination of these factors likely affects normal bacterial flora and results in *Clostridium* overgrowth.<sup>114</sup>

### 3.1.1.4 Probiotics

Probiotics have long been used to manipulate the gut flora of poultry. They work by competitive exclusion of “bad” bacteria, positive effects on the immune system, and possibly by a concept called “cross feeding,” where beneficial bacteria that exist in the intestine use substances produced by probiotics to grow.<sup>115,116</sup> Common species of bacteria used as probiotics are *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Enterococcus faecium*. As an additional point in their favor, probiotics are not expensive. A study compared 3 groups of chickens treated with a probiotic product, a bacitracin antibiotic treatment, and an untreated control group. The researchers found that the probiotic group had an improved feed/gain ratio, thereby conferring a benefit of \$0.06 per bird, while antibiotic treatment was not cost-effective compared to control.<sup>117</sup>

A newer area of research involves the use of yeasts as probiotics. Yeasts such as *Saccharomyces* produce substances called mycocins which are natural antibacterials. Yeasts can also produce enzymes that break down and inactivate bacterial toxins.<sup>118</sup>

Probiotics may also be useful in the prevention and control of coccidiosis which is a major risk factor for necrotic enteritis.<sup>119</sup>

### 3.1.1.5 Prebiotics

Prebiotics are substances added to feed that are not directly digestible by the chicken, but which are utilized by bacterial flora of the chicken’s gut. Prebiotics work by providing an energy source for beneficial bacteria such as *Lactobacillus*.<sup>120</sup>

### 3.1.1.6 Organic acid supplementation

Formic and propionic acids used as feed additives may be able to reduce the growth of bacteria such as *Salmonella* and *Campylobacter* in the gut of chickens, thereby improving overall gastrointestinal health and reducing the need for antibiotic treatment. Acetic acid is found in vinegar, and either vinegar or citric acid (also known as Vitamin C), can be added to drinking

water. A water pH of no higher than 6.0 is reported to be beneficial in decreasing intestinal disease rates among broiler chickens.<sup>121</sup> Among other proposed mechanisms, acids work by improving the digestibility of feed, and by antimicrobial action against undesirable bacteria.<sup>122,123</sup>

### 3.1.1.7 Plant extracts

Research on the use of essential oils from plants as feed additives is promising. Evidence suggests that they can play a role in combating bacterial diseases in chickens. Oils derived from thyme, oregano, and garlic show the most potential benefit, according to one review article.<sup>124</sup> Essential oils work by exerting antimicrobial, antioxidant, digestive stimulant, antiviral, antitoxin, antiparasitic, and insecticidal properties.<sup>125,126</sup> In one recent study, groups of chickens were fed a blend of essential oils, and then exposed to *Clostridium*; faced with an induced outbreak of necrotic enteritis, chickens fed essential oils experienced significantly better weight gain and intestinal health compared to control chickens.<sup>127</sup>

### 3.1.1.8 Vaccination

- ***Clostridium***: Newer strategies for formulating effective vaccines against *Clostridium* include vaccination against the toxin produced by the bacteria, rather than the bacteria itself. An active area of research also concerns the possibility of vaccinating breeding hens to provide immunity to chicks, and the use of vaccines in drinking water for young chicks.<sup>128,129</sup>
- ***Coccidia***: Because concurrent infection with coccidia is a major risk factor for necrotic enteritis, producers can use vaccination against coccidia as a tool to prevent intestinal disease in chickens.<sup>130,131</sup>

## 3.2 *In ovo* injection of antibiotics for *Salmonella* prevention in broiler chickens

The injection of antibiotics directly into eggs in broiler hatcheries constitutes another, less commonly acknowledged, routine use of antibiotics in chicken production. Many commercial breeding operations inject a small amount of gentamicin directly into the egg at the same time as vaccination of the developing chick against Marek's disease, a viral disease affecting chickens. The antibiotic is used to protect against any contamination at the time of the injection and to prevent infection with *Salmonella*, but some experts believe it may also result in a growth-promotion effect.<sup>132</sup> While *in ovo* injection is widespread in the broiler industry, "no antibiotics ever," "no antibiotics administered," and other similar labels for chicken are widely used, and those labels preclude *in ovo* use. Many major poultry producers have products which are certified for one of these labels, indicating that healthy chickens can be raised without *in ovo* antibiotic use.

### 3.2.1 Alternatives to *in ovo* injection of antibiotics for broiler chickens

Although there is little information available on this practice or alternatives, in a recent interview a poultry veterinarian discussed measures to obviate the need for routine antibiotic injection. His company found that requiring egg-producers to supply clean eggs with no visible manure, and practicing good hygiene and sterile technique while vaccinating eggs allowed for the discontinuation of preventive antibiotic injections.<sup>133</sup> An expert at the American College of Poultry Veterinarians industry conference noted that the most common source of bacterial contamination during *in ovo* injection is contaminated thawing water used to prepare the vaccine. He therefore recommends the use of low levels of chlorine in the thaw bath to reduce the incidence of contaminated vaccine.<sup>134</sup>

### 3.3 Case study- The Netherlands

The Netherlands, the EU's leading exporter of meat, reduced overall antibiotic use in food animals by 50% over three years.<sup>135</sup> Follow-up interviews with individual producers have highlighted how relatively simple changes in management and small economic investments have translated to the ability to significantly decrease overall antibiotic use.

A broiler producer with 180,000 chickens in 5 units of conventional housing was able to reduce antibiotic use on his farm by 50% between 2011 and 2014. The main changes instituted were an increased vigilance regarding temperature and climate in his poultry housing, better attention to sourcing his chicks, and improvements in the water quality. He replaced his water lines, makes sure to clean them regularly, and uses an acidifier to prevent bacterial growth. He does not contract with a hatchery so if he finds problems with a supplier of chicks, he can easily find and use a new source in the future.<sup>136</sup>

#### Methodology

A literature search was undertaken using search words: antibiotics, alternatives, prevention, and each species being studied. The Merck Veterinary Manual was consulted to find the most common diseases in each of the species, and diseases for which there were recommendations for routine preventive use of antibiotics were noted. Additional searches were conducted using those disease names. A list of all FDA-approved veterinary drugs was consulted and label claims for "prevention" in the species being studied were noted and cross-referenced with the diseases found to be likely culprits for common preventive antibiotic use. Publications from EU countries, and subject matter regarding organic production methods in the US were reviewed. Experts in food animal medicine at universities were contacted and interviewed, some of whom provided additional articles and sources. Some experts reviewed the section pertaining to their species of expertise. Individuals involved in the food industry as veterinarians or producers were contacted and interviewed. Finally, sources from EU and organic production systems were sought out and interviewed.

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- Dr. Steven Dritz, DVM, PhD, Professor Kansas State University, College of Veterinary Medicine, Swine Expert
- Dr. Guy Loneragan, BVSC, PhD, Professor of Food Safety and Public Health, Texas Tech University, Cattle Expert
- Cosimo Ferrante, Hilltown Grazers, Massachusetts, Organic Pork and Beef Producer
- Dr. Guy Jodarski, DVM, Organic Valley Cooperative, Dairy Veterinarian
- Dr. Ken Wilborn, DVM, Swine Veterinarian
- Dr. Axel Sanno, Sweden, Swine Veterinarian
- Dr. Mark Bland, DVM, Poultry Veterinarian

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Dr. Laurent consulted with NRDC staff in writing this White Paper. NRDC submitted this White Paper to the California Department of Food and Agriculture in 2017 to assist the Department in developing antimicrobial stewardship guidelines for livestock and poultry producers in California.