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Review

Opportunities for mitigating pathogen contamination during on-farm food production

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ABSTRACT

Fruits, vegetables, and meat are susceptible to contamination by foodborne pathogens at many points from production through preparation in the home. This review will largely highlight approaches and progress made in the last five years to address strategies to reduce pathogen contamination in animal production but will also touch on the emerging field of preharvest produce food safety. Mitigation strategies can be divided into those that address pathogen reduction in the environment and those that target reduction/elimination of pathogen contamination in animals or plants. The former strategy has been encompassed in studies evaluating sanitation treatments of facilities as well as in numerous epidemiologic risk assessment studies (both on-farm assessments and computer simulation models) that identify management practices that impact pathogen prevalence in animals. Interventions to significantly reduce pathogen exposure via feed or water are dependent on their role as a significant contributor to pathogen contamination in the animal production system. In addition, inconsistent results obtained with interventions of dietary additives or formulation modifications (grain versus forage; inclusion of distiller's grains) on pathogen prevalence in animals have been attributed to a range of factors including target organism, grain type, level of inclusion, the animal's health or stress level, and ability to survive the gastric acidic conditions. Recent attempts to microencapsulate organic acids or bacteriophage within feed have met with only marginal improvements in reducing pathogen carriage in animals but this approach may have greater potential with other antimicrobial additives (i.e., essential oils). Bacteriophage therapy, in general, can significantly reduce pathogen carriage in animals but based on its transient nature and the potential for development of phage-resistant subpopulations, this approach should be administered to animals just prior to slaughter and preferably to animals that are suspected "super-shedders". Other promising on-farm intervention approaches have included breeding for pathogen resistance, vaccines, and dietary bacteriocins. To optimize interventions on a cost basis, studies have also determined that application of dietary interventions at specific time points in the animal's production cycle is a useful strategy to reduce pathogen carriage (e.g., probiotics to fertilized eggs and acidified feed to fattening swine). In conclusion, applicable management and intervention strategies may vary depending on the type of food under production; however, it is important to consider from a holistic view how any new intervention strategies will affect the overall production system in order to maintain a successful, efficient food production environment.

Contents

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1. Introduction

A critical component to comprehensive farm-to-fork strategies to reduce the burden of foodborne illness is the reduction of human pathogen contamination in the food production (on the farm) environment. Considering the widespread distribution of foodborne pathogens in on-farm environments, a "zero tolerance" for pathogens in preharvest settings may be a worthy goal but one that is not realistic. In view of that limitation, the success of on-farm mitigation strategies should ultimately be evaluated relative to their impact on reducing human illnesses. In addition, adoption of mitigation strategies requires that consideration be given to both their efficacy to reduce pathogen loads in animals and on crops and the cost-effectiveness of the treatment or practice.

Given the wide diversity of production practices for domesticated animals and crops, a wide range of pathogen intervention strategies has been developed to minimize opportunities for the introduction, persistence, and transmission of human pathogens. Intervention strategies may be directed against all foodborne pathogens or target specific pathogens. In either case, there are several factors that can affect the effectiveness of a treatment, including the colonization site on the farm, level and mode of pathogen contamination, and even the time at which the subject is sampled. For example, virulence genes involved in the invasion and intracellular survival of *Salmonella* in pigs are of little importance for the colonization of tonsils, a secondary lymphoid organ that plays a key role in the persistence of this pathogen (Van Parys et al., 2010b). An evaluation of the effectiveness of an intervention should take into consideration the microbial ecology of the animal or plant to avoid unintended consequences such as an alternative pathogen colonizing the host in the absence of the targeted pathogen.

This review of mitigation strategies in food production will be divided into two major sections, those strategies that are applicable to animal production and those that are applied in the production of fruit and vegetable crops. Research addressing preharvest food safety of produce is in its infancy compared to research on pathogen contamination during animal production. Hence, most of this review will focus on pathogen control strategies in animal production and will largely highlight the approaches and progress made in the past five years. Specific strategies in animal production will include on-farm management practices that reduce exposure of animals to pathogens, treatments to reduce surface contamination and feedstuff contamination such as the effectiveness of dietary feed additives to reduce pathogen intestinal colonization, vaccination of animals, and selectively breeding for pathogen resistance. Critical to the success of any mitigation strategy is the awareness of the food producers of such practices and their benefits. Hence, several recent surveys on the willingness of farmers to adopt specific management practices will be highlighted to bring attention to the importance of including education as part of the overall approach to improving food safety on the farm. Finally, this review will conclude with the limited array of strategies used to control pathogen contamination in fruit and vegetable production.

2. Preslaughter control in animal production

Considerable research efforts have been directed during the past two decades toward preharvest control of foodborne pathogens in animal production. Several excellent reviews that summarize many of those studies have recently been published (Table 1). For purposes of this paper, we shall use those review papers as starting points to address the relative merits of the different approaches in animal production that may be used to mitigate pathogen contamination. We shall then focus within each approach on the results of recent studies that show promise for reducing pathogen contamination of animals.

3. Identification of on-farm management practices that influence the risk of pathogen contamination

One of the most common strategies to reduce pathogen contamination in animal production systems is to identify pathogen sources and farm management practices that lead to animal exposure to the pathogen on the farm. A list of selected epidemiologic risk assessment studies published in the last five years along with the farm management and feed-related factors determined to affect pathogen contamination are shown in Table 2. In general, practices that minimize interaction of the animal with humans and other animal types decrease risk. A systematic review of studies investigating feed management practices and *Salmonella* prevalence in finisher swine, however, failed to find conclusive scientific evidence that pelleted feed was a risk factor (O'Connor et al., 2008). Other studies have investigated the role of various hygienic practices as well as different feed formulations on the prevalence of contamination in the flock or herd. These factors will be addressed in subsequent sections.

Although epidemiologic risk assessment studies have provided valuable clues to the underlying influences contributing to pathogen contamination in animal production, such studies are generally costly and interruptive of routine farm practices, and confounding factors are often difficult to control. Because of these limitations, an alternative

Table 1
Selected review papers published between 2005 and 2010 that address risk factors for pathogen contamination and preharvest pathogen control strategies in animal production.

Type of animal production	Title of review paper	Reference
All	Gastrointestinal microbial ecology and the safety of our food supply as related to *Salmonella*	Callaway et al. (2008a)
	Campylobacters as zoonotic pathogens: A food production perspective	Humphrey et al. (2007)
	Reducing the carriage of foodborne pathogens in livestock and poultry	Doyle and Erickson (2006)
Ruminants	The application of food safety interventions in primary production of beef and lamb: A review	Adam and Brülisauer (2010)
	Pre-harvest interventions to reduce the shedding of *E. coli* O157 in the faeces of weaned domestic ruminants: A systematic review	Sargeant et al. (2007a)
	Preharvest control of *Escherichia coli* O157 in cattle	LeJeune and Wetzel (2007)
	Pre-harvest interventions to reduce carriage of *E. coli* O157 by harvest-ready feedlot cattle	Loneragan and Brashears (2005)
Poultry	Advances in enteropathogen control in poultry production	Cox and Pavic (2010)
	Salmonella in chicken: Current and developing strategies to reduce contamination at farm level	Vandeplas et al. (2010)
	Strategies to control *Salmonella* in the broiler production chain	Van Immerseel et al. (2009)
	Serotype-specific and serotype-independent strategies for preharvest control of food-borne *Salmonella* in poultry	Gast (2007)
	Campylobacter in primary animal production and control strategies to reduce the burden of human campylobacteriosis	Wagenaar et al. (2006)
Swine	Prevalence and risk factors for bacterial food-borne zoonotic hazards in slaughter pigs: A review	Fosse et al. (2009)
	Non-typhoidal *Salmonella* infections in pigs: A closer look at epidemiology, pathogenesis and control	Boyen et al. (2008a)
	Approaches for reducing *Salmonella* in pork production	Ojha and Kostrzynska (2007)

tool, computer simulation models, has been used with greater frequency in the last five years. Such models provide a framework for the highly managed and complex animal farms from which population dynamics of pathogens of interest can be calculated in response to management practices and food safety interventions (Table 3). For example, in an ecological metapopulation model, simulations indicated that *E. coli* O157:H7 was capable of surviving in the feedlot without growth in the cattle gastrointestinal tract, with water troughs and contaminated pen floors serving as the pathogen's primary influences on its survival and dissemination (Ayscue et al., 2009). These findings suggest that these sites are locations in feedlots where food safety interventions would have the greatest impact in reducing pathogen contamination. A simulated risk-based analysis of the Danish pork *Salmonella* program, on the other hand, revealed that the on-farm interventions that are employed have minimal impact in reducing the number of *Salmonella*-positive carcasses and the number of pork-attributable human cases (Hurd et al., 2008). One explanation for these findings is that the population of swine that was being monitored for *Salmonella* carriage was not representative of a subgroup within that population that contributed disproportionately to transmission of *Salmonella*. For example, with cattle, several research groups have identified a small sub-population of animals that harbors and fecally sheds *E. coli* O157:H7 at much higher cell numbers ($\geq 3 \times 10^4$ CFU/g feces) than most cattle (Chase-Topping et al., 2008; Matthews et al., 2006b). To illustrate the significance of this subpopulation in disseminating *E. coli* O157:H7, Matthews et al. (2006a) fit dynamic epidemiologic models to *E. coli* O157:H7 prevalence data from a cross-sectional survey of cattle farms in Scotland and determined that 80% of fecal *E. coli* O157:H7 transmission occurred from 20% of the super shedding animals. Moreover, these "super-shedders" were more likely to be fecally shedding *E. coli* O157:H7 phage type (PT) 21/28 than PT 32 (Chase-Topping et al., 2007). Comparable patterns in the distribution of PTs 21/28 and 32 between cattle and humans support the link between the bovine reservoir and human infections (Pearce et al., 2009). In light of this association, identifying factors that predispose an animal to carriage of high levels of *E. coli* O157:H7 could lead to interventions that target this subpopulation (Matthews et al., 2006a). A corollary to this approach is that applying interventions that reduce the typically low levels of *E. coli* O157:H7 carriage in cattle but do not substantially reduce the *E. coli* O157:H7 "super-shedding" by cattle will not likely have a major influence on mitigating *E. coli* O157:H7 contamination of beef. Similarly, given the wide variation in cell numbers of *Campylobacter* present in broiler cecum samples (1.7 to 8.6 log CFU/g), super-shedding *Campylobacter*-broilers may exist within flocks and if so, should be targeted in mitigation strategies (Hansson et al., 2010b).

4. Mitigating pathogen contamination through hygienic practices

Cleaning and disinfection is an integral component to biosecurity on animal farms that reduces environmental exposure of foodborne pathogens to animals (Kymäläinen et al., 2009; Van Immerseel et al., 2009). Studies on the cleanability and surface properties of new and traditional materials used in floors of cattle barns and piggeries revealed that plastic coatings, rather than silane impregnation, improved the cleanability of porous concrete but mechanical wear decreased cleanability of both floors and ceramic tile joints (used in milk rooms) (Kuisma et al., 2008; Kymäläinen et al., 2008; Määttä et al., 2009). Comparing chemicals used to disinfect and clean turkey houses revealed products containing a mixture of formaldehyde, glutaraldehyde, and quaternary ammonium compounds were more effective in eliminating *Salmonella* than products containing hydrogen peroxide and acetic acid (Mueller-Doblies et al., 2010). In contrast, a quaternary ammonium disinfectant applied to contaminated soil from poultry grow-out facilities was ineffective in decreasing *Salmonella* or *Campylobacter* populations compared to untreated soil (Payne et al., 2005). In that same study, however, disinfectants containing either phenol or a nascent oxygen compound resulted in significant reductions (0.7–0.9 log and 1.2–1.5 log CFU, respectively) compared to the control.

Disinfection of hatching eggs is also a common practice to reduce the possibility of surface pathogens being transferred to the hatching chicks. Hydrogen peroxide is used commonly by the poultry industry to treat hatching eggs but in a study comparing this agent to others, it was found to be only partially effective (70% reduction of *Salmonella*) compared to two other commercial agents that contained a biguanide (100% reduction of *Salmonella*) (Cox et al., 2007).

Application of cleaning and chemical agents on farms requires adherence to recommended protocols. In a study assessing the efficacy of cleaning and disinfection of *Salmonella*-contaminated poultry layer houses, the pathogen was not eliminated in any of the 12 laying houses examined (Wales et al., 2006). In a parallel longitudinal study of cage- and free-range layer flocks, the high variability in effectiveness of the cleaning/disinfection programs was attributed to variation in the cleaning procedures used to remove organic matter and in the application of disinfectants (Wales et al., 2007).

The influence of composition or treatment of bedding materials on pathogen contamination has also been the subject of several studies. Housing cattle in pens with pond ash versus pens surfaced with soil did not affect *E. coli* O157:H7 carriage by cattle or fecal shedding (Berry et al., 2010). Similarly, neither acidic calcium sulfate, diatomaceous earth, nor sodium calcium aluminosilicate were effective in decreasing *Salmonella* populations in chicken litter (Larrison et al., 2010). In contrast, addition of alum to poultry litter (1:10) significantly reduced both *C. jejuni* and *E. coli*

Table 2
Risk assessment studies that were published between 2005 and 2010 on the roles of various farm management and feed-related practices on the prevalence and fecal shedding of pathogens in domesticated animals.

Pathogen	Animal type, country	Risk associated with selected management and feed-related practices	Reference
Salmonella	Fattening turkeys, France	Floor disinfection decreases risk Testing for pathogen during rearing decreases risk Metering pump in house decreases risk Use of footbath increases risk	Aury et al. (2010)
	Turkeys, Canada	Increase in number of humans in contact with birds increases risk	Arsenault et al. (2007)
	Laying hen flocks, France	Housing in conventional battery cages increases risk Absence of dry cleaning in between production rounds increases risk Sampling in winter increases risk	Van Hoorebeke et al. (2010a)
	Laying hen flocks, Belgium, Germany, Greece, Italy, Switzerland	A previous *Salmonella* contamination event on the farm increases risk Age of the production system increases risk Housing system does not have a significant influence on the risk	Van Hoorebeke et al. (2010b)
	Laying hens, Belgium	Use of dead bird containers for on-floor flocks decreases risk Caged versus on-floor flocks increases risk Increase of flock size for caged flocks increases risk Proximity of delivery trucks to entrance of caged flock housing increases risk Presence of different aged birds on farm for on-floor flocks increases risk	Adeline et al. (2009)
	Broilers, Belgium	Cleaning and disinfecting by an external cleaning firm decreases risk Applying the all-in-all-out procedure decreases risk Hand washing decreases risk Previously infected flock increases risk Temporary workmen in operation increases risk	Namata et al. (2009)
	Broilers, Canada	Failure to lock chicken house increases risk	Arsenault et al., 2007
	Dairy herds, U.S.	Herd size not a significant factor Lack of use of tiestall or stanchion facilities to house lactating cows increases risk Not using monensin in weaned calf or bred heifer diets increases risk Access of lactating or dry cows to surface water increases risk Disposal of manure in liquid form increases risk Cows exposed to fields with raw manure increases risk	Fossler et al. (2005)
	Feedlot cattle, U.S.	Urea, alfalfa, clover, sorghum and antimicrobials in ration decreases risk Brewers' grains, corn gluten, cottonseed hulls in ration increases risk Sourcing animals in a pen from multiple herds of origin increases risk	Green et al. (2010)
	Finisher pigs, Denmark	Health status of herds not a significant factor Smaller herds are associated with longer high serology-positive periods Seroprevalence detected in herds during Winter/Spring took longer to return to low serology than those herds with high seroprevalence detected in Summer/Fall	Baptista et al. (2009)
	Fattening pigs, Spain	Feeding of pelleted feed increases risk Farms slaughtering more than 3500 pigs per year increases risk	García-Feliz et al. (2009)
	Pigs, Spain	Short feed withdrawal time (15 h) prior to slaughter decreases risk whereas 30 h withdrawal time increases risk	Martin-Peláez et al., 2007
Campylobacter	Turkeys, Canada	Drinking unchlorinated water increases risk Flocks housed near (≤200 m) manure heap increases risk	Arsenault et al. (2007)
	Broilers, Canada	Professional rodent control increases risk Increase in number of birds raised per year on farm increases risk	Arsenault et al. (2007)
	Broilers, Sweden	Changing footwear 2 or 3 times before entering the house decreases risk Presence of other livestock on farm or presence of domesticated or fur animals within 1 km of the farm increases risk Poor or average general tidiness increases risk	Hansson et al. (2010a)
	Broilers, Great Britain	Chlorinated drinking water decreases risk Cattle on or adjacent to the farm increases risk Previous flock positive for pathogen increases risk	Ellis-Iversen et al. (2009a)
	Broilers, Iceland	Low number (<79) of cumulative degree days above 4.4 °C decreases risk High number (>139) of cumulative degree days above 4.4 °C increases risk Maximum temperature >8.9° 2 to 4 weeks before slaughter increases risk	Guerin et al. (2008)
	Broilers, Ireland	Rodents or rodent droppings observed on farm increases risk Increase in age of birds increases risk Farms with 3 or more broiler houses increases risk Infrequent footbath disinfectant changes increases risk Sampling during summer increases risk Poorer tidiness and cleanliness of broiler houses increases risk	McDowell et al. (2008)
	Young cattle, England Wales	Indoor housing increases risk Private water supply increases risk Presence of horses increases risk Feeding hay increases risk	Ellis-Iversen et al. (2009b)
Escherichia coli O157:H7	Cow-calf operations, Canada	Presence of pigs on farm increases risk Use of corn silage supplementation in winter increases risk Increase in number of times cattle taken to a show in previous 12 months increases risk Increase in percentage of cows increases risk	Cernicchiaro et al. (2009)
	Different cattle farm types, Belgium	Farm size and introduction of new animals does not have an effect Prevalence increases with older animals for mixed dairy and beef farms and dairy farms	Cobbaut et al. (2009)
	Dairy and veal herds, Netherlands	Natural ventilation compared to mechanical ventilation increases risk At least one dog present in the stable increases risk Longer the time interval between arrival in the herd and sampling increases risk	Berends et al. (2008)

(*continued on next page*)

Table 2 *(continued)*

Pathogen	Animal type, country	Risk associated with selected management and feed-related practices	Reference
Cryptosporidium parvum	Calves, Italy	Water treatment has no effect Housing calves separately from their dams increases risk Late supply of colostrums increases risk Farms using well water increases risk	Duranti et al. (2009)
	Dairy herds, Sweden	Increase in time calf spent with cow decreases risk Frequent cleaning of single calf pens increases risk Older animals increases risk	Silverlås et al. (2009)

cell numbers within 1 month (Rothrock et al., 2008). Applying a litter acidifier to chicken litter with either used or new pine shavings reduced *Salmonella* counts through day 11 but not at day 21 (Vicente et al., 2007).

Hygienic practices not only apply for housing of animals but also during their transportation. Hides of groups of cattle that were transported for long distances (>160.9 km) were twice as likely to be *E. coli* O157:H7-positive at slaughter than cattle transported a shorter distance (Dewell et al., 2008). Ineffective cleaning and sanitation of transportation vehicles was implicated as the contributing factor to contamination of the hides of 84% of cattle by a subtype of *E. coli* O157:H7 that had not been found previously in any animal on the farm of origin (Mather et al., 2008). Cross-contamination during transport is not limited to cattle but is also a major source of pathogen contamination of poultry. Despite cleaning and sanitation, used poultry transport crates/containers are frequently found to be *Salmonella*-positive (Van Immerseel et al., 2009). A promising treatment that could dramatically reduce *Salmonella* and *Campylobacter* contamination of used poultry transport cages involves spraying chicken crates with a foam containing 3% levulinic acid plus 2% sodium dodecyl sulfate and holding for 45 min (Zhao et al., 2010). Studies revealed that using this treatment on cages after transporting chickens from the farm to the slaughterhouse reduced *Salmonella* contamination from 19% before treatment to 1% after treatment.

5. Mitigating pathogen contamination by feed and water treatments

Contaminated feed is a recognized source of both *Salmonella* and *E. coli* O157:H7 for livestock and poultry (Crump et al., 2002; Davies et al., 2004; Davis et al., 2003; Jones and Richardson, 2004; Wales et al., 2010). Hence, in the European Union, commercial animal feed production is regulated for microbiological safety and comprehensive guidelines for microbiologically safe feed production have been published in the Codex Alimentarius CAC/RCP 54-2004 "Code of Practice on Good Animal Feeding". Although application of these guidelines have resulted in a lower prevalence of feed contamination (Davies et al., 2004), the significance of reduced pathogen contamination of feed on subsequent pathogen contamination within animal operations may be dependent on the type of animal operation and its production practices. For example, Davies et al. (2004) rationalized that *Salmonella*-contaminated feed would be a major source of *Salmonella* infection in the broiler industry but would play only a minor role in the swine industry.

Table 3
Simulation model studies (2006 to 2009) that identify risk factors for pathogen contamination and evaluate the effect of pathogen control interventions in livestock.

Title of modeling paper	Reference
Modeling on-farm *Escherichia coli* O157:H7 population dynamics	Ayscue et al. (2009)
Economic and epidemiological evaluation of *Salmonella* control in Dutch dairy herds	Bergevoet et al. (2009)
Risk-based analysis of the Danish pork *Salmonella* program: Past and future	Hurd et al. (2008)
A network model of *E. coli* O157 transmission within a typical UK dairy herd: the effect of heterogeneity and clustering on the prevalence of infection	Turner et al. (2008)
Effectiveness of simulated interventions in reducing the estimated prevalence of *E. coli* O157:H7 in lactating cows in dairy herds	Ahmadi et al. (2007)
Assessing the effect of interventions on the risk of cattle and sheep carrying *Escherichia coli* O157:H7 to the abattoir using a stochastic model	Stacey et al. (2007)
A simulation model to assess herd-level intervention strategies against *E. coli* O157	Wood et al. (2007)
A semi-stochastic model of the transmission of *Escherichia coli* O157 in a typical UK dairy herd: Dynamics, sensitivity analysis and intervention/prevention strategies	Turner et al. (2006)

Studies have been conducted recently to determine the efficacy of novel treatments to decontaminate feeds and their ingredients. For example, adding a formaldehyde/propionic acid combination at 1 to 2% to *Salmonella*-contaminated (2 to 4 log CFU/g) animal protein meals eliminated detectable *Salmonella* within 24 h (Carrique-Mas et al., 2007). This synergistic antimicrobial activity between formaldehyde and propionic acid enabled the use of lower concentrations of formaldehyde which reduced fuming, operator hazard, and corrosiveness. However, such a high level of propionic acid is only suitable for use in ingredients because high concentrations of organic acids cause palatability problems in finished feed and corrosion of steel-constructed feeding equipment (Wales et al., 2010). Hence, this treatment can be used to rapidly kill *Salmonella* in a contaminated batch of ingredients.

The most common method used to reduce pathogen contamination levels in feed is heat. However, findings of a recent study revealed the time/temperature combinations of dry heat used in commercial pelleting processes would not kill high cell numbers of *E. coli* O157:H7 (Hutchison et al., 2007). Improvements to pathogen decontamination processes in feed samples should also include post-processing interventions as a significant level of recontamination occurs between the feedmill and the farm (Lo Fo Wong, 2001).

Interventions to reduce pathogen contamination of drinking water in animal production systems (chlorine, chlorine dioxide, organic acids, peracetic acid, and hydrogen peroxide) have been a focus of several recent reviews (Sparks, 2009; Wales et al., 2010). The microbiological quality of livestock and poultry drinking water has been identified as a significant risk factor in transmission of pathogens in animal production facilities (Arsenault et al., 2007; Ellis-Iversen et al., 2009a; Fossler et al., 2005; Sparks, 2009). Zhao et al. (2006) determined that treatment of water with combinations of 0.1% lactic acid, 0.9% acidic calcium sulfate, and 0.05% caprylic acid effectively reduced large cell numbers (10^5 CFU/ml) of *E. coli* O157:H7, O26:H11, and O111:NM to undetectable levels (by enrichment) within 30 min in water heavily contaminated with rumen (10:1 water:rumen) or feces (20:1 water:feces). To avoid reduced water consumption by cattle, however, they recommended that this treatment be applied periodically to drinking water troughs and then flushed, rather than being added continuously.

6. Reducing intestinal carriage of pathogens by livestock and poultry

Chemical and biological treatments of feed and water have and will continue to be an active subject of investigation for reducing intestinal carriage of pathogens within domesticated animals. Reviews addressing this broad subject specifically have been published recently (Callaway et al., 2009; Jacob et al., 2009a; Wales et al., 2010). In

general, composition of feed (grain versus forage diets, inclusion of distiller's grains, etc.), and addition of specific treatments/feed additives (ionophores, plant extracts, organic acids, prebiotics, probiotics, bacteriocins, and bacteriophages) have been investigated. These strategies will be covered in greater depth below by first summarizing briefly the predominant outcomes associated with their implementation and then highlighting how studies conducted in the past few years have added to our knowledge database.

6.1. Macronutrient diet formulation

Studies evaluating the effects of forage and grain diets on the fecal shedding of *E. coli* O157 in ruminants have been summarized by Doyle and Erickson (2006) and Jacob et al. (2009a), which are numerous and somewhat conflicting. The predominating outcome was that animals shed *E. coli* O157:H7 for a longer period of time when fed forage-fed diets compared to grain diets. Under those conditions, higher fecal pH and lower volatile fatty acid concentrations in the former diet were postulated to contribute to a more hospitable environment for *E. coli* O157:H7 survival and colonization (Jacob et al., 2009a). In some studies in which higher cell numbers of *E. coli* were observed in grain-fed diets, results were based on generic *E. coli* counts as the measured response, not on *E. coli* O157:H7. Berg et al. (2004) concluded that generic *E. coli* numbers in the hindgut of cattle should not be considered predictive of the population dynamics of *E. coli* O157:H7 in the same environment due to different responses by these organisms to diets. This study also revealed that the type of grain used in the diet may affect the fecal pathogen load with animals fed a barley grain-based diet fecally shedding higher cell numbers of *E. coli* O157:H7 and at a greater prevalence than animals fed a corn-based diet. Interestingly, when corn served as the major dietary energy source for cattle, increased pathogen fecal shedding occurred in animals receiving the diet in a moist state compared to a dry state (Cernicchiaro et al., 2010). Other macronutrient constituents in cattle diets have also been compared. Fecal shedding of *E. coli* O157:H7 decreased in feedlot cattle fed sun-dried *Ascophyllum nodosum* seaweed (Tasco-14™) compared to animals fed a barley diet (Bach et al., 2008). In contrast, prevalence of fecal shedding of *E. coli* O157:H7 by animals receiving diets containing sorghum or wheat was similar (Fox et al., 2007).

A recently recognized food safety issue with cattle diets is the increased use of fermentation by-products (distiller's grains) from corn ethanol production (National Agricultural Statistics Service, 2007). Similar to the situation with grain versus forage diets, inconsistent results have emerged for those investigations delving into an association between increased *E. coli* O157:H7 fecal prevalence and feeding distiller's grains. For example, a positive association has been found between these two factors by Jacob et al. (2008a,b), whereas a lack of association was found in other feeding trials by Jacob et al. (2009b) and Edrington et al. (2010). Most recently, Jacob et al. (2010) confirmed their earlier studies that feeding cattle 40% wet or dried distiller's grains was associated with increased *E. coli* O157:H7 prevalence, whereas at lower inclusion levels (20%), there was no significant increase in *E. coli* O157:H7 prevalence. Hence, the inconsistencies that occurred in previous studies were attributed to different inclusion levels or to variability in nutrient composition of the distiller's grains.

Dietary inclusion of different types of grains has also been shown to influence the microbial ecology of the intestinal tract of poultry and a short discussion of this topic has been included in the review of Doyle and Erickson (2006). In brief, changes in the composition of the microbial community are likely responsible for differences in colonization and survival of *Salmonella* and *Campylobacter*. For example, chickens receiving plant protein-based feed had significantly less colonization of *C. jejuni* in their ceca than birds receiving other types of feed (Udayamputhoor et al., 2003). Pathogen contamination and persistence varies depending on the types of plant protein ingested. For example, significantly less *Salmonella* colonization of the spleen, liver, and ceca occurred in broilers fed a maize-based diet compared to those receiving a wheat–rye-based diet (Teirlynck et al., 2009). In another study, there was reduced *Salmonella* colonization in broilers fed triticale-based diets than in those fed corn-based diets (Santos et al., 2008) but similar levels of colonization in turkeys fed wheat- or triticale-based diets (Santos, 2006). Changing the structure of feed also appears to affect the level of pathogen colonization, as feeding whole wheat compared to ground wheat in pelleted diets decreased intestinal colonization of *Salmonella* in broilers (Bjerrum et al., 2005), and feeding mash decreased the incidence of *Salmonella* in gizzards and ceca of broilers compared to feeding pellets (Huang et al., 2006).

6.2. Antibiotics and growth-enhancing additives

The antibiotic, neomycin sulfate, has been licensed since 1971 to treat bacterial enteritis in cattle, horses, sheep, swine, chickens and several other animals (NADA 011-315); however, legal restrictions in many countries restrict its use. Short-term feeding of this antibiotic to cattle has revealed reduced shedding of *E. coli* O157:H7 (Elder et al., 2002; Woerner et al., 2006) or no effect (Alali et al., 2004). A label change would be required before neomycin sulfate could be used to control *E. coli* O157 in cattle and concerns regarding development of pathogen resistance to the antibiotic have prevented regulatory approval (Loneragan and Brashears, 2005).

Since their regulatory approval as feed additives in the mid-1970s, ionophore antibiotics (e.g., monensin and lasalocid) have been routinely included in the diets of feedlot and dairy cattle to inhibit Gram-positive bacteria, thereby improving feed:gain ratios and production efficiency, and reducing the incidence of digestive disturbances and liver abscesses. Findings of studies conducted to determine whether ionophore supplementation facilitated a competitive advantage to the Gram-negative bacteria, *E. coli* O157, have been summarized in several reviews (Doyle and Erickson, 2006; Callaway et al., 2009), indicating that ionophores do not affect *E. coli* O157:H7 fecal shedding in cattle fed grain diets. In cattle fed forage diets, however, inclusion of monensin reduced the period of time *E. coli* O157:H7 was shed in feces (Van Baale et al., 2004), suggesting that there is a potential interaction between the type of diet and ionophore supplementation (Callaway et al., 2009).

Another growth-enhancing additive that is approved for use in the United States for pig and cattle diets is ractopamine hydrochloride. Banned for use in many other countries, including those of the European Union, this additive is a β-adrenoceptor agonist that repartitions nutrients to increase the ratio of lean-to-adipose tissue. Since the physiological counterparts to β-agonists are the hormones norepinephrine and epinephrine and such hormones have been reported to be involved in a bacterial quorum-sensing system used by *E. coli* O157:H7 (Sperandio et al., 2003), several studies have been conducted to evaluate fecal shedding of *E. coli* O157:H7 by animals receiving this additive. Initial studies revealed a decrease in fecal shedding of *E. coli* O157:H7 in sheep and cattle (Edrington et al., 2006a,b) but these findings were not substantiated in a follow-up study that occurred over a 3-year period (Edrington et al., 2009).

6.3. Chlorate and nitro-based compounds

Chlorate preparations and nitro-based compounds that target the respiratory enzyme nitrate reductase appear to act as selective toxic agents to many enteric pathogens. Whereas most beneficial bacteria in the gut do not produce nitrate reductase, most members of the family Enterobacteriaceae, including *Salmonella* and *E. coli* O157:H7, do and will intracellularly reduce chlorate to chlorite which is lethal. Anderson et al. (2005) reported that *E. coli* and *Salmonella* infections were reduced in swine, cattle, and broilers administered a chlorate product in drinking water. A subsequent study revealed there was little additional benefit to administering in the drinking water higher concentrations of chlorate

(7.5 to 60 mM) or for longer time intervals (14 to 38 h) (Moore et al., 2006). When chlorate was administered through feed, however, concentrations of 5% or greater were required to effectively reduce *Salmonella* in the crop or ceca of broilers, but average daily weight gains were reduced in broilers fed 10% chlorate (Byrd et al., 2008). When animals were preconditioned by consuming low levels of nitrate or nitroethane, the lethal effects on *Salmonella* and *E. coli* were enhanced (Anderson et al., 2006), but neither chemical has been effective in reducing *Campylobacter* populations (Anderson et al., 2006; Gutierrez-Bañuelos et al., 2007).

6.4. Phenolic antimicrobial compounds

Several recent review articles addressed the influence of dietary phenolic compounds (e.g., tannins and essential oils) on pathogen intestinal colonization and survival (Callaway et al., 2009; Jacob et al., 2009a). Plant tannins consist of both hydrolysable tannins (undergo microbial and acid hydrolysis with the release of simpler phenolics) and condensed tannins (not readily degraded in the gut). Present in some forages, tannins were determined to have an antimicrobial effect on *E. coli* O157:H7 *in vitro* and were also found to reduce the fecal shedding of generic *E. coli* when infused intraruminally to steers over a 15-day period (Min et al., 2007). Based on these findings, a hypothesis was presented that the variation in the concentration of tannins and/or lignins in forages that were tested in dietary shift studies were responsible for the inconsistent results obtained (Callaway et al., 2009). The weakness of this hypothesis is that high concentrations of tannins or lignins are typically negatively correlated with forage quality yet the greatest reductions in *E. coli* O157:H7 populations were observed when cattle were switched to high quality forages. In pigs, a hydrolysable tannin extract was determined to be ineffective for limiting *Salmonella* colonization and fecal excretion despite having a pronounced antimicrobial effect against this pathogen *in vitro* (Van Parys et al., 2010a).

It is well known that essential oils have antimicrobial properties than can inhibit foodborne pathogens in pure culture (Burt, 2004). Carvacrol, a component of essential oils of oregano, at concentrations of ≥0.05% significantly reduced *E. coli* O157:H7 populations in a rumen *in vitro* model to undetectable levels within 1 h (Rivas et al., 2009). Similarly, addition of 2% (w/v) orange pulp and orange peel, which contain essential oils, to a ruminal fluid system reduced *E. coli* O157:H7 populations from 5 log to 2 log CFU/ml and *Salmonella* Typhimurium populations from 4 log to 2 log CFU/ml (Callaway et al., 2008a). Attempts to utilize essential oils as an in-feed intervention strategy, however, have not been successful. Experimentally infected sheep receiving grass silage along with 2 ml of an essential oil (CF-SD)/day had similar populations of *E. coli* and *Listeria innocua* in their gastrointestinal tract as those being maintained on grass silage alone (Lee et al., 2009). A trial involving weanling pigs fed diets supplemented with a commercial product containing oregano oil, thyme oil, and cinnamon also was unsuccessful in controlling salmonellosis (Caballero, 2010) while a trial involving cattle revealed only marginal decreases in fecal *E. coli* populations in feces shed by animals fed the phytochemical-rich forage sainfoin (*Onobrychis viciifolia*) compared to those fed an alfalfa hay diet (Berard et al., 2009). These results suggest that the active components of essential oils may not be reaching the critical *E. coli* colonization sites in animals at concentrations that would have antimicrobial activity towards *E. coli*. It remains to be determined whether encapsulation of these ingredients would facilitate their delivery to colonization sites and improve their antimicrobial effect in live animals.

6.5. Organic acids and acidified feed

Acidification of feed and water as an intervention treatment for poultry has been studied extensively. The mechanistic basis for this treatment is that organic acids (short- and medium-chain fatty acids) enter Gram-negative bacteria in an undissociated form and then dissociate, causing the intracellular pH to decrease, anions to accumulate, and disruption of vital metabolic processes (Van Immerseel et al., 2006). Many of the studies addressing reduction of *Salmonella* colonization of broilers by organic acids were summarized in previous review articles (Doyle and Erickson, 2006; Van Immerseel et al., 2006; Wales et al., 2010), but conflicting results have been reported. Factors that may have affected the outcome include: the route of administration, the type of acid, the acid concentration, the level of pathogen challenge, and the chickens' health or stress level. Inconsistent responses of pathogens in swine to acidified feed have also been reported. O'Connor et al. (2008) determined that of 14 studies included in their systematic review of the literature, only four revealed a reduction in *Salmonella* prevalence when acidified feed was used as an intervention. Given the increased costs associated with inclusion of acid in feed during an entire growing cycle, studies were conducted in pigs to evaluate the effectiveness of short-term feeding of acidified feed or water. There was no significant reduction in *Salmonella*-positive fecal samples from finisher pigs receiving acidified drinking water (INVE NutriAd, pH 4) for 14 days prior to slaughter (De Busser et al., 2009) nor did the inclusion of a mixture of 0.4% formic and 0.4% lactic acid in the feed for 10 days affect *Salmonella* numbers in the ileum and caecum of experimentally challenged pigs (Martín-Peláez et al., 2010). In contrast, feeding pigs a ration containing 0.4% lactic acid plus 0.4% formic acid during the last 8–9 weeks of the fattening period significantly reduced *Salmonella* seroprevalence (Creus et al., 2007).

Medium-chain fatty acids, which contain 6 to 12 carbons (caproic, caprylic, capric, and lauric acids), are more antibacterial against *Salmonella* than short-chain fatty acids (formic, acetic, propionic, and butyric acids) in an *in vitro* avian intestinal epithelial cell model (Van Immerseel et al., 2004, 2006). Although incorporation of caproic acid to the feed of chicks (3 g/kg of feed) has led to a significant decrease in the level of colonization of ceca and internal organs by *Salmonella* Enteritidis at 3-day after infection of 5-day-old chicks, their affect on *Campylobacter* colonization in broilers has been inconsistent. In one study, the *C. jejuni* dose necessary to colonize 50% of broilers was estimated to be 200 times higher in broilers fed a diet supplemented with a mixture of medium-chain fatty acids (1% Lodestar™) than in control broilers (van Gerwe et al., 2010). In another study, 0.7% caprylic acid supplemented in feed for 3 days reduced *Campylobacter* populations in the ceca compared to the positive control, but did not change the cecal microbial community based on denaturing gradient electrophoresis profiles (Reyes-Herrera et al., 2010). In contrast, addition of 1% (w/w) caprylic, caproic, or capric acids to the diet of broilers for 3 days did not reduce cecal colonization by *Campylobacter* (Hermans et al., 2010).

A novel approach to administering organic acids in feed has been to microencapsulate the ingredients to prevent their absorption in the upper tract and facilitate their release further down in the gastrointestinal tract where pathogen colonization would primarily occur. However, only marginal success has been observed in studies employing this approach. In one study in which positive results were obtained, broilers fed vegetable fat-coated butyrate diets had a significant reduction of *Salmonella* Enteritidis cell numbers after 27 days compared to control birds or birds fed unprotected butyrate (Fernández-Rubio et al., 2009). In contrast, decreased environmental contamination by *S. enteritidis*-colonized broilers occurred when broilers were fed coated butyric acid compared to control broilers or broilers fed uncoated butyric acid, but cecal colonization by *Salmonella* at slaughter age was similar for all treated groups (Van Immerseel et al., 2005). The addition of butyrate-coated micro-beads to broiler feed was also unsuccessful in reducing *C. jejuni* cecal colonization and this negative response was partially ascribed to the protective effect of mucous and the rapid absorption of butyrate by the enterocytes (Van Deun et al., 2008).

Supplementation of diets with coated butyric acid; however, decreased the levels of fecal shedding and intestinal colonization of *Salmonella* Typhimurium in pigs fed these diets but had no effect on *Salmonella* colonization of tonsils, spleen, and liver (Boyen et al., 2008b).

6.6. Prebiotics

Prebiotics are non-digestible feed ingredients that pass through the upper portion of the gastrointestinal tract and are available to act as a fermentable substrate by the indigenous microflora in the lower portion of the gastrointestinal tract. Examples include fructooligosaccharides, isomaltooligosaccharides, lactose, and lactulose. An increased prevalence and cell numbers of *Bifidobacterium* and *Lactobacillus* species generally occurs in response to feeding these prebiotics that in turn serve as potential inhibitors to pathogen colonization either through competitive exclusion mechanisms or through the production of antibacterial metabolites such as lactic acid, propionic acid, or bacteriocins (Callaway et al., 2008c; Doyle and Erickson, 2006; Rehman et al., 2009; Gaggìa et al., 2010). Rehman et al. (2009) summarized the prebiotic literature applicable to broilers and concluded that the ability of prebiotics in controlling the colonization of different enteropathogens, especially *Salmonella* spp. or *Campylobacter* spp., was inconsistent. Contradictory results in swine studies on the effect of feeding prebiotics were also noted by Gaggìa et al. (2010), whereas the use of prebiotics in cattle has been limited by the ability of ruminants to metabolize most poly/oligosaccharides considered to be undigestible prebiotics in many other animals. Proper timing in feeding prebiotics may be necessary to capture their benefits as evidenced by the findings of no significant reduction in *Salmonella* fecal populations of broilers continuously administered a mushroom extract but significant reductions of *Salmonella* populations if the mushroom extract was administered only during the first 21 days of the 49 days feeding trial (Willis et al., 2009).

The mannan-oligosaccharides do not strictly meet the definition of prebiotics but are administered as feed additives in a similar manner to prebiotics. Although these compounds do not enrich the growth of indigenous microflora, they can reduce *E. coli* populations by binding to *E. coli* in the intestinal lumen and blocking the bacteria's adhesion to epithelial cells (Baurhoo et al., 2007). Studies have revealed the number of birds colonized by *Salmonella enterica* serovar Enteritidis was less in mannan-oligosaccharide-fed birds compared to birds fed a control diet (Fernandez et al., 2000).

Prebiotic feed additives may provide the greatest beneficial effect in animal production systems when farm animals are subjected to environmental stresses. For example, critical stress points in the production cycle of swine are during weaning (separation from the sow, characterized by end of the lactation immunity and transition onto a diet based on plant polysaccharides) and post-weaning (transport to a production farm). Decreased feed intake occurs at these critical points that lead to imbalances in the intestinal ecosystem and susceptibility to pathogen colonization. Incorporating 4% sugar beet and chicory inulin fructo-oligosaccharides into the diet of newly weaned pigs increased the endogenous bifidobacteria in newly weaned pigs (Modesto et al., 2009), thereby providing an environment that would be less hospitable to *Salmonella*. For laying hens, a critical period for increased susceptibility to *Salmonella* colonization occurs during forced molting through feed withdrawal, a management practice that stimulates multiple egg-laying cycles. In a study of molting hens fed alfalfa diets containing 0, 0.375 and 0.75% of fructo-oligosaccharides, it was revealed that *Salmonella* colonization was reduced in hens fed the prebiotics in molt diets (Donalson et al., 2008).

6.7. Probiotics and synbiotics

Feeding competitive exclusion (CE) or probiotic (direct-fed) microbial cultures is yet another potential intervention to reduce pathogen carriage by livestock and poultry. The treatment involves administering one or more strains of nonpathogenic bacteria to animals such that the competitive microbes colonize the gastrointestinal tract and create inhospitable conditions for foodborne pathogens. CE cultures contain a mixture of undefined microbes, whereas probiotic cultures contain microbes of known identity and are often further characterized regarding their lack of virulence and antibiotic resistance genes. For example, CE products are typically isolated from the gastrointestinal tract of the animal species that will be treated and consist of undefined mixed bacterial cultures. In contrast, probiotic cultures utilize one or more well-defined strains that have been cultured separately prior to their application.

Several CE and probiotic products are commercially available (Callaway et al., 2008c); however, CE products are not approved for use in livestock and poultry in the U.S. because of concerns regarding the potential for virulence and antibiotic resistance genes being transmitted by the undefined microbes. Recent research has therefore focused largely on the development and validation of probiotic products (Table 4) due to the many concerns associated with CE products which in part are delineated by Wagner (2006). Importantly, U.S. regulations require that the bacteria present in such products be identified but by the very complex nature of CE cultures, the types and numbers of bacteria present in the mixture could vary from lot-to-lot. Other concerns with CE products are the potential presence of antimicrobial resistance genes and the possibility of transferable virulence genes in the unidentified/undefined bacteria of CE products.

Microorganisms having promise as animal feed probiotics are mainly bacterial strains belonging to the genera *Lactobacillus*, *Enterococcus*, *Pediococcus*, and *Bacillus*, although yeasts such as *Saccharomyces* have also been used (Gaggìa et al., 2010; Vandeplas et al., 2010). *Bifidobacterium* species are used as probiotics in humans but the few studies where this organism has been studied as a probiotic to control pathogens in animals have included *Lactobacillus* spp. in the treatment (Gaggìa et al., 2010). *Enterococcus faecium* and *E. faecalis* have been the subject of many clinical trials in pigs (Gaggìa et al., 2010). These organisms, however, have not been included in the list of microorganisms that would be considered for the status of Qualified Presumption of Safety (QPS) by the European Food Safety Authority due to the possibility that some strains may carry transmissible antibiotic resistance genes (EFSA, 2007). Proper labeling, including the name of the exact taxonomic species, for any commercial probiotic cultures is essential. A recent study that examined the microbial composition of several commercial probiotic products found microbes other than those claimed on the label (Wannaprasat et al., 2009). Labeling should also include a “best-before” use date that would address the viability of the cultures under defined storage conditions (Gaggìa et al., 2010).

There are several other benefits to feeding of probiotic cultures to animals in addition to the control of foodborne pathogens in the gastrointestinal tract. These have been summarized by Gaggìa et al. (2010) and include improved feed conversion with subsequent enhanced growth rates. This latter benefit is a principal reason why *Lactobacillus* NP-51 is used in many feedlots across the United States and Canada as the increase in growth efficiency economically balances the cost of its inclusion in cattle rations (Callaway et al., 2008c).

Screening of bacterial cultures for antimicrobial activity, survival in the gastrointestinal tract (bile and acid resistance), adhesion capability, and antibiotic susceptibility is often done as part of the process to select for effective probiotic cultures. Antimicrobial activity is typically determined by applying potential probiotic isolates on an agar plate containing a “lawn” of the pathogen of interest and selecting those that produce large clear zones indicating inhibitory or bactericidal activity. Zhang et al. (2007a) determined that the best approach for obtaining probiotic candidates highly inhibitory to *Salmonella* and *C. jejuni* from chickens was to isolate the bacteria from ceca under anaerobic conditions. Using such an approach, free-range chickens from family farms were determined to be better donors of

Table 4
Selected examples of in vivo and *in vitro* studies (2007 to 2010) evaluating the pathogen reducing efficacy of competitive exclusion, probiotic, or synbiotic treatments.

Treatment	Challenge conditions	Observed effects	Reference
Poultry			
Oral inoculation on day after hatch with 2×10^8 of *L. reuteri* R-17485 or *L. johnsonii* R-17504	Oral inoculation on day 2 after hatch with 10^4 CFU *S.* Enteritidis	On day 6 after hatch, 10-fold lower counts for *S.* Enteritidis in caeca, liver, and spleen of chicks receiving treatments compared to controls.	Van Coillie et al. (2007)
Day-of-hatch chicks were administered by gavage 0.5 ml of probiotic culture containing *L. salivarius* and *Streptococcus cristatus* (10^6 to 10^8 CFU/chick)	Mixture of *S.* Enteritidis, *S.* Kentucky, and *S.* Typhimurium were administered by gavage to 3-day old chicks (10^4 CFU/chick)	On day 7 after challenge, the average reduction over two trials in *Salmonella* carriage for treated versus control chickens was 41% and 3.1 log CFU/g	Zhang et al. (2007b)
Oral administration of 10^4, 10^6, or 10^8 CFU of a *Lactobacillus*-based probiotic culture (FM-B11, Ivesco, LLC, Springdale, AK) to each chick 1 h postchallenge	Day-of-hatch chicks were each challenged with 7.5×10^3 CFU of *Salmonella* Enteritidis by oral gavage in a 0.25 ml volume	Doses of 10^6 and 10^8 both significantly reduced *S.* Enteritids recovery in cecal tonsils 24 h after treatment compared with controls (15 vs. 85% positive) but 10^4 CFU did not significantly reduce *S.* Enteritidis recovery	Higgins et al. (2008)
One treated group received *E. faecium* (5×10^9 CFU/pig/day) in drinking water, a second treated group received feed containing 10^6 CFU *B. licheniformis* and *B. subtilis*/g feed	Pigs inoculated intranasally with a 2 ml suspension (10^9 CFU/ml) of *S.* Typhimurium on day 0 and euthanized on day 12	Fecal and tissue concentrations of *S.* Typhimurium were similar for pigs receiving probiotics either in water or feed compared to control pigs	Spiehs et al. (2008)
Commercial probiotic (PrimaLac, Star Labs, St. Joseph, MO) containing $>10^8$ CFU/g of *L. acidophilus*, *L. casei*, *Bifidobacterium thermophilus*, *Enterococcus faecium*) fed ad libitum to broiler chickens for 49 days	Natural exposure	Prevalence of *C. jejuni* in broilers fed treated feed was 44% compared to 56% in broilers fed control diet	Willis and Reid (2008)
Daily feeding (100 mg/kg feed) with Toyocerin (containing 10^{10} viable spores of *Bacillus cereus* var. *toyoi* NCI-MB 40112/CNCM I-1012/g) until slaughter on day 42 for broiler chickens or day 28 for White Leghorn chickens	Broiler chickens orally challenged on either day 3, 7 or 14 with 10^6 CFU/chick. White Leghorn chickens orally challenged on day 7 with 10^8 CFU/chick.	*Salmonella* was not detected in Toyocerin-treated broiler birds whereas 42% of untreated birds were still positive for *Salmonella*. In Leghorn chickens, 38% of birds from the Toyocerin-treated group were *Salmonella*-positive, whereas 63% of birds were still *Salmonella*-positive in the untreated control treatment	Vilà et al. (2009)
Broiler chickens were treated by gavage daily for 15 days with a suspension of *Bifidobacterium longum* PCB 133 or *Lactobacillus plantarum* PCS 20 (10^8 CFU)	Natural exposure	Fecal samples from chickens fed *B. longum* showed a significant one-log reduction in *C. jejuni* compared to fecal samples from control chickens	Santini et al. (2010)
Swine			
A *Lactobacillus* mixture (2 strains of *L. murinus* and one strain each of *L. salivarius* subsp. *salivarius*, *L. pentosus*, and *Pediococcus pentosaceous*) were cultured and fed through a milk base (10^9 or 10^{10} CFU/day) to weaned pigs for 30 days	6 days into the feeding trial, animals were challenged orally with 10^8 CFU *S. enterica* serovar Typhimurium for 3 consecutive days	At 15 day post-infection, *Salmonella* count in control fecal samples were 200-fold higher than fecal samples from probiotic-treated samples; however, at 23 day post-infection, no significant difference in numbers of *Salmonella* occurred	Casey et al. (2007)
Nonradiolabeled *Lactobacillus rhamnosus* LGG, *Bifidobacterium lactis* Bb12, or their combination was added (100 μl of 10^7 to 10^8 CFU/ml) to pathogen-contaminated mucus and inhibition of pathogens was calculated	Radiolabeled *S. enterica* serovar Typhimurium was applied to pig mucus obtained from duodenum, jejunum, ileum, ascending colon, transcending colon, and descending colon (10^8/ml)	Percent pathogen inhibition ranged between 63 and 82%, 33 and 84%, and 71 and 86% for LGG, Bb12, or combination treatments, respectively	Collado et al. (2007)
From the day of birth, piglets were inoculated orally each day for 7 days with 2 ml of *L. plantarum* (10^8 CFU/ml). For selected groups, piglets were administered orally Maldex 150 (maltodextrin) and Raftifeed IPX (fructooligosaccharide) 4 times a day at a dose of 0.3 g	Piglets were challenged orally on day 5 with 5 log CFU of *E. coli* O8: K88ab:H9/piglet	*E. coli* O8:K88 adhering to the jejunum and colon mucosa were significantly lower when animals received both the probiotic (*L. plantarum*) and prebiotic (Maldex 150 and Raftifeed IPX) compared to probiotic alone	Nemcová et al. (2007)
Cattle			
L. acidophilus NP-51was dissolved in water and sprayed on feed such that steers obtained 10^9 CFU daily	Natural exposure	The probability for NP-51-treated steers to shed *E. coli* O157:H7 in 2002 and 2003 was 13 and 21%, respectively, compared with 21 and 28% among controls	Peterson et al. (2007)
Steers fed a diet with administered target values of either 10^7, 10^8, or 10^9 CFU of *L. acidophilus* NP51/steer/day	Natural exposure	*Salmonella* was 48% less likely to be shed in feces of cattle receiving the high dose whereas fecal samples from steers receiving low and medium doses did not exhibit significant differences in *Salmonella* recovery. *E. coli* O157 was 74% and 69% less likely to be recovered in feces from animals receiving the high and low diets, respectively, compared with controls	Stephens et al. (2007)
Treated steers were fed throughout the finishing period a diet containing Bovamine® at 10^9 CFU of *L. acidophilus* (LA 51) and 10^9 of *P. freudenreichii* (PF 24)	Natural exposure	The probability of recovery of *E. coli* O157:H7 from the feces of treated and control steers was statistically different at 34 and 66%, respectively. The probability of recovery of *Salmonella* from the feces of the control (14%) and treated steers (11%) was statistically similar. The probability of new infections with *Salmonella* was statistically reduced in treated cattle compared to controls	Tabe et al. (2008)

potential probiotic bacteria strongly inhibitory to both *Salmonella* and *Campylobacter* than were chickens from commercial farms and broiler chicken research centers. Under the assumption that the *in vitro* selection process may bias the selection of strains and potentially overlook strains that may be competitive in vivo, Stephenson et al. (2010) utilized an in vivo screening approach in which chickens were fed diets containing mixtures of lactic acid bacteria and then enterobacterial repetitive intergenic consensus-PCR was used to

identify those rifampicin-resistant isolates that persisted in the chickens.

Critical components of effective probiotic treatments include the dose, duration of treatment, timing of treatment relative to pathogen exposure, health and growth of the animal, and method of application of the treatment (Doyle and Erickson, 2006; Gaggìa et al., 2010). For example, Higgins et al. (2008) observed that doses of 10^6 and 10^8 CFU of a *Lactobacillus* probiotic culture both significantly reduced *S.* Enteritidis in cecal tonsils of broilers 24 h after treatment compared to controls whereas a lower dose of 10^4 CFU did not significantly reduce *S.* Enteritidis colonization. As another example, exposure of an animal to probiotic bacteria early in its life was beneficial to the establishment of a favorable niche for those bacteria through the modulation in gene expression in intestinal epithelial cells (Siggers et al., 2007). Inoculating a probiotic culture (*Enterococcus faecium*, *Lactobacillus casei*, and *L. plantarum*) into fertilized eggs and subsequent challenge with *S.* Enteritidis at hatching led to elimination of the pathogen in the crop and in the cecum of the chicks at 7 and 21 days of age (Leandro et al., 2010).

Application of both probiotics and prebiotics to a host animal is defined as synbiotics (Gaggìa et al., 2010). Several studies have revealed a synbiotic treatment was more efficacious in promoting growth or reducing *Salmonella* in poultry than an individual prebiotic or probiotic treatment (Awad et al., 2009; Revolledo et al., 2009; Vandeplas et al., 2009). In cattle, however, the use of prebiotics or synbiotics has been limited due to the ability of ruminants to degrade most prebiotics. Although development of rumen-protection technology to prevent prebiotic degradation in the rumen may circumvent this limitation (Callaway et al., 2008b), a drawback to the synbiotic approach is the potential for many prebiotics to increase satiety and subsequently decrease feed intake and weight gain in animals (Daubioul et al., 2002).

6.8. Bacteriophages

Bacteriophages are naturally occurring viruses that infect specific bacteria and reproduce within them. Two groups of phages occur and differ with respect to their ability to lyse their host (Johnson et al., 2008) In the case of temperate phages, integration of the phage genome into the host cell DNA occurs where it replicates along with the host cell DNA without lysing the bacterial host. Lytic phages, on the other hand, destroy the host cell DNA, replicate within the cell, and then lyse the host cell releasing numerous daughter phages. To capitalize on this natural predation process, application of lytic bacteriophages, specific for foodborne pathogens, has been suggested as a potential intervention strategy to reduce pathogen contamination in animals in preharvest settings.

One of the unique characteristics of bacteriophages is their narrow specificity. Bacteriophages can target below the bacterial species level, sometimes infecting only a few strains within a species. For example, phages active against *Salmonella* Typhimurium and isolated from feces of finishing swine did not affect *Salmonella* of a variety of other serotypes, including those of other group B serotypes (Callaway et al., 2010). A study by Sheng et al. (2006) employing two phages illustrated the diversity of specificity of available bacteriophages. Phage KH1 did not form plaques on any of the non-O157 *E. coli* isolates, whereas phage SH1 formed plaques on 18 of 120 non-O157 *E. coli* isolates. Phage specificity is determined largely by the interaction between binding sites on their tail fibers and one or more receptors (lipopolysaccharides, proteins, capsular polysaccharides, flagella, or pili) on the cell surface of the host bacterium. To avoid unwanted effects on commensal flora, a narrow spectrum of activity is desirable. Hence, the ideal treatment would include either a bacteriophage targeting common surface receptors on several pathogens or a mixture of phages, each targeting a specific receptor on one or more pathogen subtypes.

In addition to the specificity of a bacteriophage, the bacteriophage's acid resistance is another variable that should be evaluated prior to conducting in vivo studies. Acid resistance of the phage is critical as oral application requires that the phage tolerate gastric passage and maintain a sufficient concentration for activity at the pathogen's location to enable infection and lysis (Dini and de Urraza, 2010). A buffering agent may be added to the bacteriophage mixture or given to the animal immediately after the phage treatment to minimize adverse effects of the acidity (Atterbury et al., 2007; Niu et al., 2008). More recently, encapsulation of phage for protection in harsh environments has been evaluated. For example, free phage Felix O1 was not detectable after a 5-min exposure to pH values below 3.7, but when micro-encapsulated by a chitosan–alginate–$CaCl_2$ polymer, the phage PFU decreased only by 0.7 log after a 5-min exposure to a pH of 2.4 (Ma et al., 2008). Similarly, when phages were microencapsulated using a sodium alginate-based method with or without poly-L-lysine, the phages remained stable at both 4 °C and 22 °C with no appreciable decrease in titer for up to 14 days (Zhang et al., 2010). However, studies on the efficacy of these protective coatings have yet to demonstrate any improvement in reducing pathogen carriage. Encapsulated bacteriophages orally fed to feedlot cattle either in a gelatin capsule or top-dressed on their feed did not reduce fecal shedding of *E. coli* O157:H7 compared to untreated cattle (Stanford et al., 2010).

Ideally, phages should amplify themselves and kill the target hosts by repeated cycles of replication until the host is eliminated. In studies conducted to date, however, phage treatments have for the most part reduced the number of pathogens compared to untreated controls but did not eliminate the bacteria (Table 5). One explanation to account for this self-limiting outcome is that the numbers of pathogens are reduced to a 'phage proliferation threshold' beyond which the numbers of target bacteria are insufficient to sustain phage replication (Payne and Jansen, 2003). As a consequence, these reductions are often transient and pathogen levels return to pre-treatment levels (Andreatti Filho et al., 2007), thereby developing an oscillating equilibrium between predator and prey (Johnson et al., 2008). In another possible scenario, co-existence of relatively stable numbers of host cells and phages may occur when phage-resistant subpopulations emerge. In using bacteriophage therapy to reduce *Salmonella* colonization of broiler chickens, studies revealed applying larger phage titers resulted in a greater proportion of resistant salmonellae than in chickens receiving lower phage titers (Atterbury et al., 2007). These investigators as well as others (O'Flynn et al., 2004) observed that phage resistance was not maintained for long periods and reverted to being phage sensitive. Alternatively, to mitigate the emergence of phage resistant strains, phage cocktails containing multiple phages can be applied. Interestingly, larger phage dosages will not necessarily have greater efficacy in reducing pathogen populations. Callaway et al. (2008d) revealed that feeding a 1:1 ratio of phage to *E. coli* O157:H7 was more effective in reducing the pathogen populations in ruminant gastrointestinal tracts than higher ratios (10:1 or 100:1). The investigators postulated that the reduced efficacy at higher host/phage ratios may be due to competitive interference between phages, also known as "lysis from without", wherein simultaneous infection of a host cell by multiple phages leads to cell lysis.

Due to the transient nature of bacteriophage therapy (1 to 3 days), incorporation of this approach may be most advantageous if administered immediately prior to slaughter and to animals that may be suspected 'super-shedders'. If effective reductions in intestinal carriage of 1 to 2 logs could be achieved, that in turn should reduce the pathogen load entering the food chain. Unfortunately, applying treatments just before slaughter would not affect farm prevalence of pathogens, environmental dissemination of the organism, or hide or feather contamination.

6.9. Bacteriocins

Nontoxic, ribosomal-produced antimicrobial peptides secreted by bacteria and known as bacteriocins are one of the more recent

Table 5
Selected examples of studies (2006 to 2008) evaluating the pathogen reducing efficacy of bacteriophage treatments.

Treatment	Challenge conditions	Observed effects	Reference
Poultry			
1 h postchallenge, chicks were treated via oral gavage with either one of two bacteriophages (CB4Ø or WT45 Ø, 8 log PFU/chick) or a combination of both	Day-of-hatch chicks were challenged orally with 9×10^3 CFU/chick *Salmonella* Enteritidis	All treatments significantly reduced *Salmonella* Enteritidis in cecal tonsils at 24 h (45 to 70% prevalence) compared to control (100% prevalence). No significant differences were observed at 48 h following treatment	Andreatti Filho et al. (2007)
2 days after pathogen challenge, the broilers were administered by oral gavage one of three bacteriophages (1 ml of 9 or 11 log PFU bacteriophage/ml antacid suspension)	Broilers were challenged by oral gavage at 36 days of age with 1 ml 8 log CFU/ml suspension of *Salmonella enterica* serotypes Enteritidis, Hadar, and Typhimurium	Cecal populations of the three *Salmonella* serotypes were not reduced significantly 6 days following treatment at the lower dosage. At the higher dosage, *S.* Enteritidis and *S.* Typhimurium populations were reduced within 24 h by ≥4.2 and ≥2.2 log CFU compared with controls. *S.* Hadar colonization was unaffected by treatment	Atterbury et al. (2007)
Ruminants			
3 days after challenge, sheep were treated with a singe oral dose of CEV1 bacteriophage (~10^{11} PFU)	Each sheep was inoculated by oral gavage with 10 log CFU *E. coli* O157:H7 EDL 933/animal	Treated sheep showed a 2-log reduction in intestinal (cecum and rectums) *E. coli* O157:H7 levels within 2 days compared to levels in the controls	Raya et al. (2006)
7 days after challenge, a mixture of phages (SH1 and KH1, 25 ml of 10 log PFU/ml) was delivered into the anus of each steer and gently swabbed with a sponge against the wall of the rectoanal junction. In addition, phages were maintained at 6 log PFU/ml in the drinking water of the phage treatment group	A mixture of 4 strains of *E. coli* O157:H7 was given to steers (10 log CFU/steer) as a single oral dose.	Numbers of *E. coli* O157/swab were significantly less among the phage-treated steers than among the control group from day 1 through day 10 posttreatment ($P<0.05$). The phage treatment did not clear *E. coli* O157 from four of the five treated calves	Sheng et al. (2006)
Challenged sheep were given a phage cocktail (8 phage isolates with activity against *E. coli* O157:H7, 9 log PFU/sheep) at 48 and 72 h	Sheep were inoculated by oral gavage with *E. coli* O157:H7 933 (10 log CFU/sheep)	24 h after phage treatment, populations of inoculated *E. coli* O157:H7 were reduced 1-log CFU/g in both the cecum and rectum compared to control samples	Callaway et al. (2008d)
On days −2, 0, 2, 6, and 9, steers were dosed orally with a 100 ml of 2% sodium bicarbonate followed by a mixture of 4 *E. coli* O157-specific phages (11 log PFU/steer)	On day 0, each steer was inoculated orally with a mixture of five strains *E. coli* O157:H7 (9 log CFU/steer)	Prevalence of *E. coli* O157:H7 in rectoanal mucosal swab samples collected on 16 occasions over 12 weeks was reduced from 70.3% in control to 55.5% in treated samples	Niu et al. (2008)

advances under investigation as an on-farm intervention in animal production. These antimicrobials generally possess a net positive charge and an amphipathic structure that facilitates interaction with negatively charged microbial membranes or other cellular targets (Sang and Blecha, 2008). Many of the bacteria included in probiotic intervention treatments (e.g., *Lactobacillus*, *Lactococcus*, *Pediococcus*, *Carnobacterium*, *Enterococcus*, *Escherichia*, and *Bacillus*) produce bacteriocins and thus as natural metabolites, they already likely play an important role in the ecology of the microbial intestinal system (Svetoch and Stern, 2010). Another positive attribute for these types of antimicrobials is that their spectrum of activity ranges from narrow to wide providing an opportunity to select one bacteriocin that would be active against a specific type of pathogen but that does not affect the normal microflora of the animal.

Bacteriocins differ from antibiotics in a number of properties including: 1) antibiotics are secondary metabolites of the cell, whereas bacteriocins are directly produced via translation of ribosomes; 2) bacteria are susceptible to the antibiotics they produce but have protective mechanisms to limit harm from self-produced bacteriocins; 3) attachment of bacteriocins to bacteria is non-specific and does not require receptors; 4) bacteriocins interact directly with bacterial membranes to generate pores, ion leakage, and death, whereas the mechanism of action of antibiotics is generally through disruption of anabolic pathways; and 5) development of resistance by pathogens to bacteriocins is much less frequent than to antibiotics (Svetoch and Stern, 2010).

Traditionally viewed as being largely active against related Gram-positive bacteria or Enterobacteriaceae with minimal inhibitory concentrations in the nanomolar range (Sang and Blecha, 2008), bacteriocins are continuously being isolated and identified and make up a highly diverse family of proteins in terms of size, microbial target, mode of action, and release and mechanism of immunity. A database devoted strictly to cataloguing bacteriocins contained as of July 2009, 177 bacteriocin sequences, of which 156 were the products of Gram-positive bacteria and 18 from Gram-negative bacteria (Hammami et al., 2010). Approved for commercial use as a biological preservative, nisin is the most widely recognized bacteriocin and is used in the food processing industry. In animal production, however, only limited studies have determined the potential for bacteriocins to reduce foodborne pathogen contamination (Table 6). Based on these studies, four different bacteriocins were determined to be highly effective in reducing *C. jejuni* contamination of chicken broilers and turkey poults. Although the efficacy of bacteriocin therapy was first explored in young birds, later studies revealed that short-term treatment (3 days) applied to mature (ready-to-slaughter) birds were also easily applied and effective in reducing cecal colonization of both *C. jejuni* and *Salmonella* and hence would likely lead to reduced carcass contamination in the processing plant.

To provide greater specificity to bacteriocins, novel bactericidal protein complexes are being generated for possible evaluation as antimicrobials in animal production settings. Specificity is incorporated into the complex by fusing tail fibers from bacteriophages specific to a pathogen to a high-molecular weight bacteriocin, known as an R-type pyocin. Pyocins are produced by many strains of *Pseudomonas aeruginosa* (Michel-Briand and Baysse, 2002). Using such an approach, an engineered pyocin, termed AVR2-V10, killed 100% of diverse *E. coli* O157:H7 isolates in the absence of any release of Shiga toxin, as is often the case with many antibiotics, and could kill *E. coli* O157:H7 on beef surfaces (Scholl et al., 2009). The utility of feeding these engineered bacteriocins to animals, however, has not been reported to date.

6.10. Immunotherapy

Passive immune protection conferred to animals to prevent colonization of specific pathogens involves the feeding of antibodies that have

Table 6
Selected examples of studies (2005 to 2008) evaluating the pathogen reducing efficacy of bacteriocin treatments in poultry.

Bacteriocin, source organism	Treatment	Challenge conditions	Observed effects	Reference
B602, *Paenibacillus polymyxa* NRRL B-30509	B602 was encapsulated in polyvinyl-pyrrolidone, incorporated into feed at 250 mg/kg, and then fed to 7-day-old chicks for 3 days	Day-of-hatch chicks were challenged by oral gavage with individual strains of *C. jejuni* (8 log CFU/chick)	Population reductions of *C. jejuni* in cecums of treated chicks ranged from 4.6 to 6.3 log CFU/g compared to control chicks	Stern et al. (2005)
B602, *P. polymyxa* NRRL B-30509 or OR-7, *Lactobacillus salivarius* strain NRRL B-30514	B602 or OR-7 was encapsulated in polyvinyl-pyrrolidone, incorporated into feed at 250 mg/kg, and then fed to 10-day-old poults for 3 days	3 day post-hatch, turkey poults were challenged by oral gavage with 3 strains of *C. coli* (6 log CFU/poult)	In each of the 3 separate trials, the 3-day treatment with either bacteriocin reduced ceca *Campylobacter* to nondetectable levels (<2 log CFU/g) compared to non-treated poults having levels of 5–6 log CFU/g	Cole et al. (2006)
OR-7, *Lactobacillus salivarius* strain NRRL B-30514	OR-7 was encapsulated in polyvinyl-pyrrolidone, incorporated into feed at 250 mg/kg, and then fed to 7-day-old chicks for 3 days	Day-of-hatch chicks were challenged by oral gavage with individual strains of *C. jejuni* (8 log CFU/chick)	Bacteriocin treatment consistently reduced colonization in cecum of 10-day old chicks at least one millionfold compared with levels found in untreated groups	Stern et al. (2006)
Enterocin E-760, *Enterococcus* strain NRRL B-30745	Enterocin was mixed with commercial feed at various levels (125 mg, 62, 5 mg, and 31.2 mg/kg feed) and treated feed was given to 4-day-old chicks for 3 days	Day-of-hatch chicks were challenged by oral gavage with two strains of *C. jejuni* (6 log CFU/chick)	*C. jejuni* was not detected in any of the treated chicks whereas the untreated chicks were colonized with 8 log CFU/g cecum	Line et al. (2008)
	In a second trial, 39-day-old chicks were admininstered for 4 days feed containing 125 mg enterocin/kg	In the second trial, colonization by *C. jejuni* occurred naturally	Untreated birds were all colonized with *C. jejuni* with an average of 6.2 log CFU/g cecum whereas *Campylobacter* was only detected in 1 of 10 birds given treated feed	
E 50–52, *Enterococcus faecium* NRRL B-30746	E 50–52 was encapsulated in polyvinyl-pyrrolidone, incorporated into feed at 125 mg, 62, 5 mg, and 31.2 mg/kg feed, and then fed to 4-day-old chicks for 3 days	Day-of-hatch chicks were challenged by oral gavage with two strains of *C. jejuni* (6 log CFU/chick)	All three treatment levels with E 50–52 eliminated detectable (<2 log/g cecum) levels of *C. jejuni* in 15-day-old chicks whereas the untreated birds were colonized with 8.4 log CFU/g cecum	Svetoch et al. (2008)
	In a second trial, E 50–52 was provided in drinking water to challenged birds for either 1, 2, or 3 days (12.5 mg/L water)	In the second trial, 35–41 day-old broilers (environmentally colonized by *C. jejuni*) were challenged with 10–11 log CFU *Salmonella enteritidis*	Oral treatment with E 50–52 reduced both *C. jejuni* and *S. enteritidis* by more than 5 log in the ceca	

been manufactured in biological entities to combat those pathogens. One of the most cost-effective methods to manufacture and recover those antibodies for use as a therapeutic agent is to vaccinate hens and harvest the large quantities of antibodies (IgY) transferred to their eggs (Schade et al., 2005). The efficacy of such antibodies in reducing pathogen carriage, however, has yielded conflicting results. When 3 day-old chicks were challenged orally with *S.* Enteritidis (6 log CFU/chick) and then received SE-specific-IgY-containing egg yolk in drinking water (5:1 v/v) for 25 days, the treated birds had significantly less fecal shedding (0 versus 14% of chicks) and lower cell numbers of *S.* Enteritidis in the cecum (0.27 versus 3.98 log CFU/g) (Rahimi et al., 2007). In a subsequent *in vitro* study, it was determined that SE-specific IgY blocked the adhesion of *Salmonella* to Caco-2 intestinal cells (Chaighoumi et al., 2009). In contrast to these promising results, prophylactic use of crude anti-*S.* Typhimurium IgY supplemented in poultry starter feed, did not prevent or reduce colonization in chicks (Pavic et al., 2010).

6.11. Vaccines

Vaccination of animals to prevent their carriage of foodborne pathogens is another intervention technique by which the immune system of animals may be exploited. Review articles addressing this intervention technique have been published recently (Doyle and Erickson, 2006; Lin, 2009; Denagamage et al., 2007; Potter et al., 2008); therefore, for the purposes of this review, only selected studies published after 2007 were summarized in Table 7. In general, live vaccine strains offer better protection against pathogens compared to inactivated vaccines due to the induction of both cell-mediated immunity as well as humoral activity (Boyen et al., 2008a; Meeusen et al., 2007; Penha Filho et al., 2009). Despite this advantage, some public health decision makers consider live vaccines less safe than killed or subunit vaccines, particularly when genetic manipulation has been used to produce the live vaccine (Barrow, 2007). As a result, only a few live *Salmonella* vaccine strains are registered and commercially available for use in poultry in Europe (Barrow, 2007; Vandeplas et al., 2010). To enhance the efficacy of killed vaccines, researchers have developed adjuvants that would augment the immunostimulation of killed vaccines (Barrow, 2007; Cox et al., 2006; Potter et al., 2008). Three promising adjuvant systems have been reviewed by Potter et al. (2008) including DNA-containing CpG motifs, cationic host defense peptides, and synthetic single-stranded RNA and imidazoquinolines.

A major limitation of vaccination as an intervention strategy is that immunized animals generally produce antibodies against the vaccine strain and therefore it is difficult to distinguish using serological tests vaccinated animals from pathogen-infected animals exposed in the field. In one study in which this was not the case, a vaccination protocol for pigs led to significant protective immunity without producing detectable levels of ELISA antibodies (Husa et al., 2009). When challenged with *S.* Typhimurium, however, rapid antibody production and detection occurred with seroconversion of >95% of pigs occurring 9 days after challenge. Another approach used to distinguish vaccinated animals from animals field-exposed to pathogens has been to vaccinate with attenuated *Salmonella* strains having single or multiple defined mutations in the bacterial genome. For example, vaccination of chickens with a guanine auxotrophic Δ*guaB* and a nonflagellated Δ*fliC* double mutant resulted in absence of antiflagellin antibodies in sera of immunized animals that could be used to distinguish between field-infected animals and animals vaccinated with *S. enterica* serovar Enteritidis live-vaccine strains (Adriaensen et al., 2007). Unfortunately, this study also exemplified the relatively poor success in immunizing animals to prevent intestinal contamination with non-host-specific *Salmonella* serotypes. More specifically, the double mutant vaccine protected against systemic infection but not against intestinal colonization.

A number of factors have been cited as influential in the efficacy of a vaccine treatment including: the challenge strain, the infection dose(s), the age of the animal, the breed/bird line, and the route of administration (Barrow, 2007). With respect to the vaccination route,

Table 7
Selected examples of studies (2008 to 2010) evaluating the pathogen reducing efficacy of on-farm animal vaccination treatments.

Origin of vaccine	Challenge conditions	Treatment and observed effects	Reference
Poultry			
Commercial vaccines were used in this study including the inactivated *S.* Enteritidis-based vaccine CEVA Biomune (Layermune SE; Lenexa, USA) and the live *S.* Gallinarum-based vaccine CEVA Campinas (Cevac SG9R; Campinas SP, Brazil)	At 12 weeks of age, commercial layers and broiler breeders were challenged orally with *S.* Enteritidis PT4 (8 log CFU/chicken)	At 2- and 5-day post-challenge, cecal *Salmonella* contamination in vaccinated layers were >2 log CFU/g less compared to unvaccinated layers. Cecal contamination in breeders were not significantly different at 2-day post-challenge whereas *Salmonella* levels in cecum were close to 4 log CFU/g less in breeders vaccinated with both live and inactivated vaccines compared to unvaccinated breeders	Penha Filho et al. (2009)
Live *Salmonella* Gallinarum mutant strain with deletion on genes *cob*S and *cbi*A, that are involved in the biosynthesis of cobalamin.	At 45 day of age, birds from commercial white lines of chickens were challenged orally with *S.* Enteritidis (8 log CFU/chick)	At 2- and 5-day post-challenge, levels were <2 log CFU/g in the cecum of chickens treated with a two dose regimen (vaccination at 5 and 25 days of age) compared to 4 and 5 log CFU/g cecum in the untreated chickens, respectively	Penha Filho et al. (2010)
Swine			
Commercial vaccines were used in this study including the avirulent live *Salmonella* serovar Choleraesuis vaccines Enterisol SC-54 (Boehringer, Missouri) or Argos SC/ST (Intervet Inc., Delaware).	On day 43 following vaccination of treated groups, pigs were challenged intranasally with *S.* Typhimurium (10 log CFU/pig)	Both vaccines conferred cross-protection to *S.* Typhimurium with greater cross-protection by SC-54	Husa et al. (2009)
Cattle			
Commercially available *S. enterica* subunit vaccine (AgriLabs Inc., Missouri)	Natural exposure	Fecal shedding of *S. enterica* was similar for vaccinated and nonvaccinated cows on each of the collection dates (day 0 — initial vaccination, day 14 — booster vaccination, day 28 and day 70)	Heider et al. (2008)
Commercially available *S.* Newport vaccine containing siderophore receptor and porin (SRP) proteins (AgriLabs Inc., Missouri)	Natural exposure	No significant difference occurred in prevalence of *Salmonella* Agona recovered from feces of vaccinated cattle (2-dose regimen) relative to the prevalence of recovery from feces of control cattle for any of the 3 collection times (up to 90 days of lactation) during the study	Hermesch et al. (2008)
Live attenuated *Salmonella* Dublin mutant N-RM25	On days 14 and 20 following oral and intramuscular injection, respectively, calves (≤6 weeks age) were orally challenged with *S.* Dublin (9 log CFU/animal)	No *Salmonella* was isolated from the gut at 18 days post-challenge using either oral or intramuscular injection	Mizuno et al. (2008)
Commercially available *E. coli* O157:H7 SRP vaccine	Natural exposure	Prevalence of *E. coli* O157:H7 in fecal and rectoanal mucosal swab samples collected over 57 days were reduced significantly when cattle had been vaccinated subcutaneously with 3 ml of SRP vaccine compared to samples from nonvaccinated cattle (17.7% vs. 33.7%; $p<0.01$). A 3 ml dose of SRP vaccine also reduced the number of days cattle tested positive for *E. coli* O157:H7 (2.4) compared to control (4.2)	Fox et al. (2009)
Commercially available *Salmonella* SRP vaccine	Natural exposure	Dairies that practiced whole-herd vaccination with the vaccine had a lower prevalence of *Salmonella* in feces (7.6%) than herds that were not vaccinated (39.2%)	Loneragan et al. (2009)
Commercially available *E. coli* O157:H7 Type III secreted proteins vaccine	Natural exposure	A 3-dose regimen of vaccination significantly reduced the probability for beef feedlot cattle to shed *E. coli* O157:H7 by 65% compared to placebo-treated cattle	Moxley et al. (2009)
Commercially available *E. coli* O157:H7 Type III secreted proteins vaccine	Natural exposure	*E. coli* O157:H7 was recovered from 4.8%, 9.1%, and 12.3% of fecal samples from pens containing vaccinated cattle only, pens containing half vaccinated and half nonvaccinated cattle, and pens containing nonvaccinated cattle, respectively	Smith et al. (2009)
Commercially available *E. coli* O157:H7 SRP vaccine	Natural exposure	On day 98, there was an 85% reduction in shedding of *E. coli* O157:H7 when cattle were administered the SRP vaccine compared to control animals. Vaccination with SRP was also associated with a 98% reduction in concentration of *E. coli* O157:H7 in fecal samples (0.8 vs 2.5 log MPN/g feces)	Thomson et al. (2009)

oral vaccination is considered to be one of the most promising antigen delivery methods for directly stimulating mucosal immunity in the gut (Gerdts et al., 2006). A common problem associated with oral delivery of live vaccines, however, is that fecal shedding of vaccine organisms occurs following vaccination. For example, fecal shedding of the vaccine strain occurred for up to 3 days in 5 of 18 calves vaccinated with a DNA adenine methylase deficient *S. enterica* serovar Typhimurium vaccine (Mohler et al., 2006). Similarly, fecal shedding of *S.* Dublin occurred over an 8-day period following oral administration to calves of the *S.* Dublin vaccine, whereas fecal shedding did not occur in intramuscularly vaccinated calves (Mizuno et al., 2008).

A systematic review of studies conducted to evaluate the efficacy of vaccination to reduce *Salmonella* prevalence in market weight, finisher swine concluded that significant reductions, although incomplete, were achieved (Denagamage et al., 2007). Using a deterministic compartmental model, the greatest impact on reduction of endemic prevalence and in turn prevention of human *Salmonella* infections was achieved when these imperfect *Salmonella* vaccines reduced the length of the infectious period (Lu et al., 2009).

Vaccines based on subunit antigens have been used in intervention studies for *E. coli* O157:H7 carriage by cattle (Table 7). The two major antigens that have been used are: 1) type III-secreted proteins; and 2) siderophore receptor and porin (SRP) proteins. The premise for using the type III-secreted proteins is that they are involved in *E. coli* O157 attachment to mucosal epithelial cells and antibody binding to these proteins would prevent colonization. The premise for using SRP proteins is that antibody binding to SRP proteins on the pathogen's cell membrane restricts the pathogen's ability to acquire iron from the environment thereby placing it at a disadvantage in the microbial consortia within the gastrointestinal tract (Hermesch et al., 2008). The

potential advantages of using subunits as vaccines are increased safety and less antigenic competition, since only a few components are included in the vaccine, and the ability to differentiate vaccinated animals from infected animals. The disadvantages are that subunit vaccines generally require strong adjuvants and the duration of immunity is generally shorter than obtained with live vaccines. As a result, only moderate success has been achieved with these vaccines and it is believed that they will reach their full potential when used in combination with other intervention strategies. As a single intervention strategy, however, vaccination was determined to be a cost-effective approach for preventing *E. coli* O157:H7 illness in humans even when vaccine costs ranged from $2.29 to $9.14 per animal (Withee et al., 2009). Greater success is likely on the horizon for vaccines as new targets for developing vaccines are identified. One such target could be the regulator, SdiA, that is responsible for sensing acyl-homoserine lactones that are prominent in the bovine rumen and aids enterohemorrhagic *E. coli* in adapting to such environments (Hughes et al., 2010).

6.12. Culling

The process of removing domesticated animals from a herd or flock based on specific criteria is known as culling. Primarily applied to remove diseased or underperforming animals from the population, culling may also be used as a mitigation strategy for reducing foodborne illness associated with meat consumption by applying to the culled population processing interventions that would otherwise not normally be employed. For example, Golden et al. (2008) suggested that shell eggs produced immediately following molt could be designated for in-shell pasteurization. Similarly, Wagenaar et al. (2006) suggested that meat from *Campylobacter*-infected flocks could be either frozen or treated with chemicals to reduce the contamination. In terms of the benefits of culling, a probabilistic model illustrated that upon diverting all *Campylobacter*-positive flocks to freezing, 43% fewer illnesses would occur (Lindqvist and Lindblad, 2008). Integral to this strategy, however, is the identification of populations that test positive for the pathogen or that would likely be positive based on the previous history of the production facility or the animal's physiological condition. As an example, studies revealed that herds with laboratory-confirmed clinical cases of salmonellosis had a higher prevalence of *Salmonella* fecal shedding than herds that had only *Salmonella*-positive environmental samples (Cummings et al., 2010). In the absence of any animals exhibiting disease symptoms, *Salmonella* fecal shedding by asymptomatic animals is more difficult to detect without routine monitoring. Identification of asymptomatic animals is crucial as evidenced by a report that PFGE patterns from nine *Salmonella* serovars obtained from asymptomatic dairy cattle and farm environments were indistinguishable from PFGE patterns from human isolates obtained in New York (Rodriguez-Rivera et al., 2010). Culling practices, however, have not always been proven to be legitimately based on sound science. For example, selling damaged chicken wings in the EU is prohibited on the grounds that their microbial contamination would be greater than undamaged chicken wings (Anon, 2007). To refute that predication, a study conducted by Malpass et al. (2010) found no compelling evidence to suggest that either farm- or factory-damaged chicken wings should be categorized as unfit for human consumption.

6.13. Breeding

The genetic composition of poultry plays a key role in their resistance to colonization by *Salmonella* or *C. jejuni* (Swaggerty et al., 2009); hence, animal breeding for improving their innate immune response is a potential on-farm intervention strategy. Studies have revealed differences in cecal colonization of *C. jejuni* in two different commercial broiler lines (Li et al., 2008). Subsequent studies revealed that a dramatic up-regulation in lipid, glucose, and amino acid metabolism occurred in line B chickens with little or no change in immune host defenses, whereas the more resistant line A birds had an up-regulation in lymphocyte and T-cell activation (Li et al., 2010). A similar type of differential response to *S.* Enteritidis by two commercial broiler lines was observed (Chiang et al., 2008). In this case, *Salmonella* infection induced a stronger, up-regulated gene expression in the heterophils of line A than line B, and these genes included several components in the Toll-like receptor signaling pathway and genes involved in T-helper cell activation. Heterophils of the Fayoumi line (a line that has not undergone commercial selection) that were stimulated with *S.* Enteritidis also had increased expression of genes encoding for interleukin-6, interleukin-10, granulocyte macrophage-colony stimulating factor, and transforming growth factor-β-4 compared to broiler and Leghorn line heterophils that had decreased or no changes in the cytokine gene expression levels (Redmond et al., 2009). This unique response is suggestive that breeding programs conducted over the past years to increase meat production has been at the expense of the immune system that influence pathogen colonization of broilers. Recent research has therefore focused on shifting the measures used for progeny selection, including fast growth and ability to increase cytokine and chemokine responses that are needed to resist colonization by foodborne pathogens (Swaggerty et al., 2009). Along with these efforts, it has been determined that the rooster has more influence than the hen in determining heterophil response and resistance to *S.* Enteritidis and *C. jejuni* (Li et al., 2008; Swaggerty et al., 2009).

6.14. Multiple interventions

The rationale for incorporating multiple interventions into a comprehensive program to mitigate pathogen contamination of animals on the farm is that the interventions target different colonization sites or mechanisms the pathogen uses to facilitate its colonization within the animal. The projected outcome of such an approach would be that additive or even synergistic reductions in pathogen colonization would occur. Such an event occurred when chicks were exposed to both a probiotic treatment (Broilact, Orion Corp, Finland) and three *Salmonella*-specific bacteriophages prior to being challenged with *S.* Enteritidis (5 log/chick). Seven days after this challenge, the incidence of *S.* Enteritidis in ceca from these probiotic-, bacteriophage- and combination-treated chicks was 76%, 80%, and 39%, respectively (Borie et al., 2009). Combination treatments, however, have not always generated additional reductions in pathogen contamination. For example, Andreatti Filho et al. (2007) treated chicks with a bacteriophage mixture and/or a commercially available probiotic (Floramax-B11, IVS-Wynco LLC, Arkansas) prior to challenge with *S.* Enteritidis (3 log CFU/chick). The incidence of *S.* Enteritidis in cecal tonsils 24 h after challenge was 36% and 48%, respectively; however, the incidence in chicks receiving the combination treatment was 36%. Given these different outcomes utilizing similar treatment combinations (probiotics and bacteriophages), additional studies are needed to identify the mechanistic basis for the different responses as it will aid in future selection of multiple on-farm interventions to reduce pathogen carriage by farm animals.

7. Dissemination of pathogen intervention information and education of stakeholders

Development of scientifically validated on-farm interventions that reduce pathogen contamination in animals and farm environments does not ensure their implementation by stakeholders. A lack of knowledge by the stakeholders as to factors incorporated into risk analyses that relate to the biology and epidemiology of foodborne pathogens (Sargeant et al., 2007b) makes it difficult for the stakeholder to determine the relevancy of scientific studies to their operations. As an example, only 21% of Canadian broiler producers who participated in an on-farm food safety program called “Safe, Safer, Safest” were even aware that *Campylobacter*

could be transmitted from contaminated chicken meat to humans (Young et al., 2010b). In many cases, stakeholders recognize their insufficient knowledge and seek additional input from other sources to interpret food safety policy. To illustrate this point, a survey of Canadian dairy producers revealed they rated veterinarians as very knowledgeable about on-farm food-safety programs (91%) and hence were a favored (73%) source of information regarding food safety (Young et al., 2010a). Deferring to the advice of one's veterinarian, however, does not ensure that food safety practices will be adopted. English and Welsh cattle farmers who had not adopted disease control programs identified their veterinarian as the key motivator, whereas consumer-demand and financial rewards or penalties were significantly associated with farmers who intended to adopt control programs (Ellis-Iversen et al., 2010). Hence, recognition of the stakeholder's knowledge barriers and key motivating forces that would lead to operational changes is one component to developing effective programs for disseminating information related to food safety interventions. Another component recently explored has been the merits to shifting communication from a one-way to a two-way pathway. More specifically, engagement of stakeholders in a participatory process during the development of risk analyses provides for consideration of hazards they view as important (Barker et al., 2010). Such shared responsibility by stakeholders is presumed to contribute to their subsequent support of policies that arise from those risk analyses and ultimately their willingness to adopt food safety management guidelines contained within those policies.

8. Preharvest pathogen control in produce production

During the past two decades, the fresh fruit and vegetable industry has rapidly evolved resulting in increased retail and food service sales. Accompanying this growth has been an increased number of outbreaks of illness associated with fresh produce consumption (Lynch et al., 2009). According to Sivapalasingam et al. (2004), produce-associated outbreaks increased from 0.7% in the 1970s to 6% in the 1990s. More recent data from the Center for Science in the Public Interest database indicated produce outbreaks accounted for 13% of foodborne illness outbreaks in the U.S. between 1990 and 2005 (deWaal and Bhuiya, 2007). In Australia, by contrast, only 4% of all foodborne outbreaks reported from 2001 to 2005 were attributed to fresh produce (Kirk et al., 2008).

Mitigation strategies to reduce on-farm pathogen contamination of ready-to-eat produce crops have primarily focused on prevention of contamination in the field. To date, field or post-harvest interventions that will ensure complete elimination of contaminated product are either not available or would not be accepted by the consumer. Consequently when produce crops that are consumed raw are suspected to have been contaminated, either they are not harvested or they are diverted to products that would be heated prior to consumption.

One of the first guidance documents to address on-farm practices that would minimize introduction of pathogens to produce fields was written by the U.S. Food and Drug Administration in conjunction with the U.S. Department of Agriculture and the fresh produce industry. Entitled "A Guide to Minimize Microbiological Food Safety Hazards for Fresh Fruits and Vegetables", the material in this document constituted the basis for Good Agricultural Practices (GAPs) for the produce industry (U.S. FDA, 1998). Addressing common areas of concern in the growing, production, and distribution of fresh produce, this guide focuses on risk reduction, not risk elimination. Another distinguishing feature of this document is that the recommendations are very broad and subjective to encompass the broad spectrum of commodities and growing practices in the industry.

8.1. Good Agricultural Practices (GAPs)

Since the introduction of the FDA GAPs guidance document, many other guidance documents have been prepared either by the industry or with input from the industry that address GAPs for specific commodities, such as tomatoes, leafy greens, and melons (CLGMB, 2010; United Fresh Produce Association, 2008; U.S. FDA, 2009a,b,c, 2010). Developed largely in response to repeated outbreaks associated with these types of produce, the documents include specific guidelines that are applicable to each produce group. The extent of coverage varies with each document in that some guidelines are more narrowly focused such as covering only primary production and handling, whereas other documents also include packing or transportation operations. Five major categories are generally included in GAPs for on-farm operations: 1) soil and fertilizers; 2) irrigation water; 3) field and harvest personnel; 4) equipment; and 5) management. With some of the issues, specific guidance (metrics) are provided but they have not always been scientifically validated and may be revised as new data become available. As an example, in the leafy greens marketing guidance document, it is advised that no crop should be harvested within 1.5 m of any fecal material in the field (CLGMB, 2010). A report posted on the California Leafy Greens web site summarizing a recent study, however, indicated that current guidelines underestimate the potential area that can be affected by feces in a sprinkled-irrigated field (Fonseca et al., 2009). In that report, it was revealed that *E. coli* could be recovered as far away as 2.4 m from the feces source (0.9 m more than the recommended metric) when sprinklers operated in the presence of wind speeds of <19.3 kph. Additional studies will need to be conducted to determine the risk associated with dissemination of pathogens from point sources of contamination in the field.

8.2. Pre-harvest produce interventions

There have been limited studies addressing interventions that may be applied to produce to either prevent or eliminate pathogen contaminations on plants or in soil. A promising approach has been the application of competitive bacteria to plant surfaces. The rationale for this approach is that many types of epiphytic bacteria on plant surfaces serve naturally as a deterrent to foodborne pathogen survival and growth in the phyllosphere (Heaton and Jones, 2008) and may therefore be used as biocontrol agents. Laury et al. (2010) electrostatically sprayed lactic acid bacteria (9 log CFU/ml) onto spinach plants in the field either at planting or during the first 4 weeks of the growing cycle. It was determined that when *E. coli* O157:H7 (3 log CFU/ml) contaminated spinach plants and Lactiguard™ was applied once during the 4-week interval, *E. coli* O157:H7 populations on treated spinach plants were 0.8 to 2.1 log CFU less than populations on control plants. Similarly, alfalfa seeds, pre-inoculated with *S. enterica*, *L. monocytogenes*, or *E. coli* O157:H7, had significantly less growth of the pathogens during sprouting when *Lactobacillus lactis* AA4 was applied to seeds either as individual strains or in combination with *Enterococcus mundtii* CUGF08 compared to untreated seeds (Feng et al., 2010). Differences in responses have been observed when single versus multiple competitive bacterial strains were included in the biocontrol treatment of alfalfa seeds/sprouts (Matos and Garland, 2005). For example, *Pseudomonas fluorescens* 2–79 provided the greatest prevention of growth of *Salmonella* at 1 day of alfalfa growth (>4 log) whereas at day 7, an inoculum of microorganisms derived from market sprouts provided a greater level of protection (>5 log less *Salmonella* than the uninoculated control).

Biocontrol of *E. coli* O157:H7 in soil has also been addressed recently by Yossa et al. (2010). *E. coli* O157:H7 populations in soil were 5 log CFU/g less than controls after 24 h of incubation at room temperature when 2% cinnamaldehyde, an essential oil, was mixed into the soil. In contrast, mixing of 2% eugenol into the soil had little effect on *E. coli* O157:H7 populations after 24 h of incubation at room temperature, compared to the control.

8.3. Interventions to minimize introduction of pathogens

Soil amendments, particularly manure or improperly treated manure, have been implicated as a potential source of pathogen contamination of produce fields. In the absence of any physical or biological treatment, it is recommended that raw manure be stored for a sufficient period of time to ensure inactivation of pathogens prior to its application on fields that could be growing ready-to-eat produce. Aerobic thermophilic composting of animal manure can produce a safe soil amendment for use in produce production; however, incorporation of insulating covers on static compost piles can enhance the microbiological safety of the compost material at surface sites (Shepherd et al., 2009). Studies have revealed *E. coli* O157:H7 was detected in uncovered heaps through 120 days, whereas it was below detectable limits after 21 days of composting in covered heaps. Bacteriophage treatment of compost pile surfaces is also worthy of consideration as more than a 2 log reduction of *Salmonella* occurred within 4 h compared to the controls (Heringa et al., 2010). One limitation of that treatment, however, was that the moisture content needed to be at 30% or above in order that sufficient water be available in the compost to transport the bacteriophages to uninfected pathogen cells. Moisture availability would not be a limitation if wastes were stored as slurries and were treated with bacteriophages as studies have revealed bacteriophage treatment of manure slurries reduced *E. coli* O157:H7 populations by 5- and 4-log within 3 summer days or 1 spring/fall day, respectively (Jiang, 2010).

9. Concluding comments

Effective food safety interventions to reduce or control foodborne pathogens are needed throughout the food continuum, from the farm to the end user. Current production and processing procedures for livestock and poultry and fresh fruits and vegetables do not have sufficiently robust food safety interventions to ensure pathogen-free fresh meat and produce products. Since there is no single widely accepted food safety intervention that will eliminate pathogen contamination of fresh and minimally processed foods, the application of effective food safety interventions must be at the farm and additional interventions need to be thereafter at subsequent stages of food processing, packaging, distribution, retail, and home or foodservice establishments. Combinations of interventions may be needed throughout the food continuum to provide continuous reduction in pathogen contamination and ultimately the incidence of foodborne illnesses.

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