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Food Safety From Farm to Fork

Interventions on farms and feedlots can improve U.S. meat and poultry safety

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Any opinions and conclusions expressed herein are those of The Pew Charitable Trusts and do not necessarily represent the views of the above individuals.

Comments from federal agencies

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For further information, please visit:
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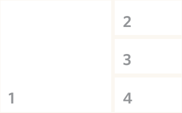

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Overview

Contaminated meat and poultry products are responsible for an estimated 2 million illnesses in the United States each year, and amount to more than 40 percent of all bacterial foodborne diseases.[1] The annual cost of illnesses—for instance, direct medical costs, lost income, and productivity—attributable to consumption of these foods has been estimated at about $2.5 billion for poultry, $1.9 billion for pork, and $1.4 billion for beef.[2]

Livestock species often harbor foodborne pathogens. Infected animals may or may not show signs of infection, which can make it challenging to identify them. Depending on the pathogen involved, meat from infected animals may, in rare cases, already be contaminated with the pathogen before slaughter. More often, however, foodborne pathogens are restricted to the gastrointestinal tract of animals but are not present in the muscles, the main component of edible meat. Contamination of meat most commonly occurs during or after slaughter through contact with fecal material, animal hides, gastrointestinal content, lymph nodes, or the slaughter environment. While certain interventions and management practices during and after harvest can reduce contamination risks, many food safety experts suggest that to better protect public health, the U.S. needs a comprehensive approach to meat and poultry safety that begins at the farm level.

The Pew Charitable Trusts examined food safety control measures currently used on farms and feedlots or that might be employed in the future. This report assesses pre-harvest interventions aimed at reducing the level of the major foodborne pathogens—*Salmonella, Campylobacter,* and *Escherichia coli (E. coli)* O157:H7—that can lead to the contamination of meat from poultry, swine, and cattle. These pathogens are included in this examination because they account for a substantial proportion of infections linked to meat and poultry consumption, and research on pre-harvest interventions has focused primarily on them.

Identifying potential pre-harvest measures, however, is just a first step in effectively controlling food safety hazards and allowing further improvements to public health. While existing pre-harvest interventions can reduce pathogens to some extent, a comprehensive approach is necessary to significantly reduce contamination. This must include safety measures before, during, and after harvest—a true farm-to-fork approach.

Controlling pathogens at the farm level can help reduce human illnesses beyond meat and poultry products. Due to the risk of manure runoff and secondary contamination of downstream products, illnesses linked to the consumption of other food items, such as fresh produce or water, could also be reduced.

Ultimately, the impact of a particular intervention in reducing contamination will depend on how widely it is adopted and how effectively it is used. Each might not be cost-effective, practical, or even successful for every species, pathogen, and production system. Interventions have to be timed appropriately to allow maximum efficacy, and not all interventions are compatible with each other.

As discussed in detail in Appendix H, several countries have successful, comprehensive food safety control programs that include a strong pre-harvest component, often partnerships between government and the livestock industry, initiated using government appropriations and sustained with industry dollars. These programs are science- and risk-based, and periodically evaluated for efficacy and cost-effectiveness; they demonstrate that success requires substantial time and resource commitments, as well as teamwork and continuing buy-in from all stakeholders. They also show that success is possible and that the public health benefit can be substantial.

Pew identified the following key characteristics shared by effective pre-harvest programs. They:

- Typically begin with the breeding herds or flocks from which the production animals are derived.
- Rely on feed safety, biosecurity, and pathogen surveillance as well as specific pre-harvest interventions.
- Combine multiple interventions, which improves the efficacy of the programs, makes use of potential synergisms between interventions, and reduces the ability of the pathogen to evolve mechanisms to circumvent an intervention.
- Target interventions to the animal species and production system, allowing implementation when and where they work best and are successful, feasible, and cost-effective. With the exception of biosecurity (measures to prevent introduction of infectious agents, such as quarantine, access restrictions, and vermin control), which is widely accepted as a prerequisite for animal production, no single intervention is entirely successful in combating all pathogens in all species.

Adoption and implementation of on-farm control measures are, in many cases, hindered by economic challenges. For example, although consumers may derive benefits from cattle being vaccinated against a potentially deadly foodborne pathogen, Shiga toxin-producing *E. coli*, the cow-calf operation that would have to make the investment may not be able to gain any direct benefit from the vaccination because the operation does not market the animals straight to consumers. In addition, companies that market animals to consumers may derive limited benefits from such vaccination because they are unlikely to promote the increased safety of their food to consumers, and regulatory challenges may be limitations rather than an expansion of technical and scientific knowledge.

This report provides a summary of pre-harvest interventions for use in poultry, cattle, and swine. Several appendices offer an in-depth analysis of the topics discussed here, providing the scientific support for the conclusions stated. Detailed information on the mode of action as well as the efficacy, benefits, and limitations of individual interventions for the different species and production systems are provided. These appendices also provide context for the role of pre-harvest food safety in the food chain and identify data gaps and areas for further research as well as highlight potential roadblocks to implementation. They also review successes achieved in other countries with pre-harvest interventions.

Recommendations

To improve food safety in the U.S. through pre-harvest interventions, Pew makes the following recommendations:

To funding agencies such as U.S. Department of Agriculture's National Institute of Food and Agriculture

1. Extend funding opportunities to support:
    a. Relevant research, particularly into biosecurity and best management practices, which are foundational to pre-harvest food safety and effective across a wide variety of species, production systems, and pathogens but to date have not been a focus of most scientific research.
    b. Large field trials on commercial operations for interventions that may be promising but currently lack efficacy data, particularly for hard-to-address issues such as *Campylobacter* in poultry and swine or *Salmonella* in swine.
    c. Research on commercial operations to optimize application protocols, such as timing vaccination to maximize efficacy and cost-effectiveness.

2. Study the basic science, mechanism of action, ancillary benefits, and potential unintended consequences associated with poorly understood yet promising interventions such as pre- and probiotics, including alternative approaches that may reduce the need for antibiotics. Similarly, studies should also evaluate the cost-effectiveness of promising pre-harvest interventions as this will be a critical prerequisite for successful implementation.
3. Designate more funding to evaluate potential synergistic or antagonistic effects among interventions, the underlying drivers of variability in efficacy across farms and operations, and the cost-effectiveness of interventions, including potential incentives to increase uptake of the interventions by producers.
4. Consider incentives to spur research and development in the pre-harvest food safety area, by providing, for instance, more grants and fostering public-private partnerships.

To federal agencies

1. Provide incentives for the implementation of pre-harvest food safety interventions, be they regulatory or economically motivated. In particular, consider strategies that lead to improvements in biosecurity and management practices as part of these incentives.
2. Expand the use of innovative tools such as risk assessments to systematically synthesize pertinent data and prioritize when and where interventions should be applied.
3. Improve the regulatory approval processes in such a way that product safety, consistency, efficacy, and quality can be guaranteed while making sure promising products can reach the market in a timely fashion. In particular, consider the value of technological advancements such as whole-genome sequencing for overcoming traditional challenges to regulatory approval.
4. Improve collaboration and communication among all stakeholders (farmers, meat producers, consumers, regulatory agencies, academic researchers, the pharmaceutical industry) to increase the availability and use of promising interventions. In particular, strengthen interagency collaborations to leverage technical expertise across and within organizations and closely align animal health and food safety responsibilities, even if they rest in different entities such as USDA's Food Safety and Inspection Service and Animal and Plant Health Inspection Service.

To industry

1. Emphasize the use of individual pre-harvest interventions as one part of a herd health management program, in the context in which they will be used (for example, animal species and age group, production system), along with potential synergisms or antagonisms between interventions. Evaluate whether ancillary benefits may be achieved, such as improvements in overall animal health that may reduce treatment costs and animal losses.
2. Provide adequate biosecurity, feed and water safety, and basic animal health standards as a prerequisite for the production of meat and poultry on farms and feedlots, even if biosecurity may be more challenging to ensure in some production systems (such as pasture-based systems).
3. For industries in which a small number of breeding herds or flocks give rise to the production animals, consider the feasibility and potential value of pathogen eradication programs upstream, in elite herds or flocks, and create incentives for such programs where feasible.

To all stakeholders

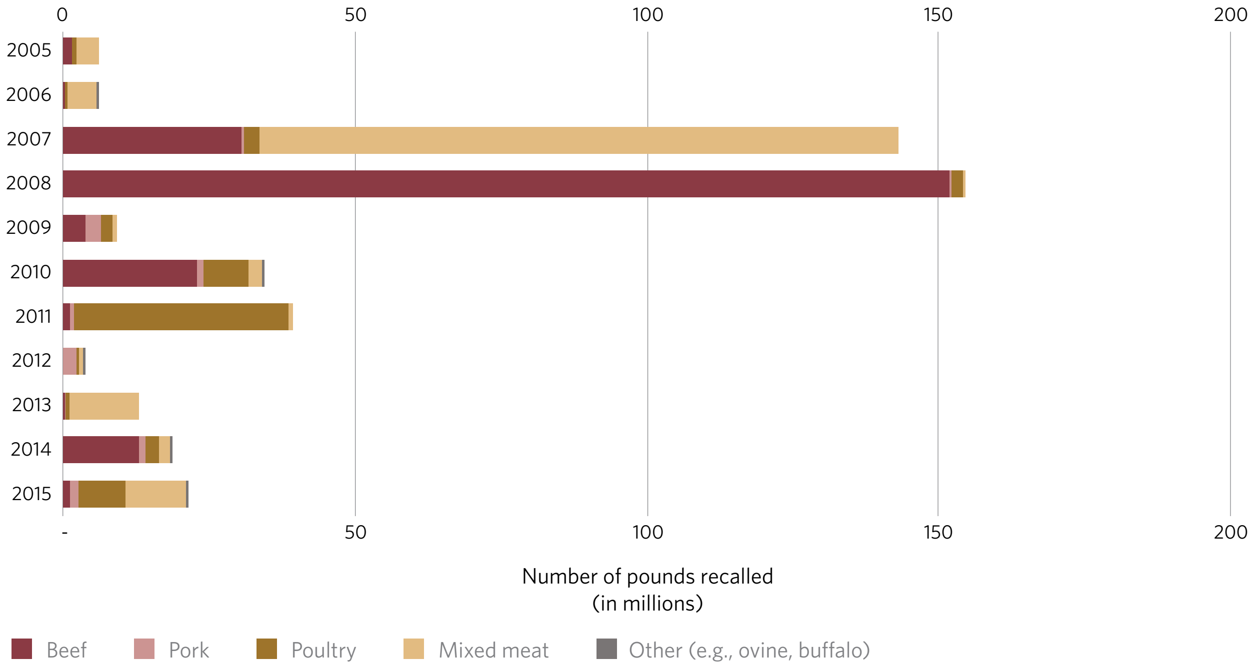
1. Encourage data sharing between industry, academia, governmental researchers, and regulatory agencies to allow data on the efficacy and safety of these products from all settings to be used to the greatest extent possible. Public-private partnerships may be the most feasible approach to closing some of the data gaps that currently hinder the development and use of pre-harvest interventions. This will require overcoming legal and logistical challenges such as privacy and transparency concerns and information technology infrastructure compatibility.

The importance of meat and poultry as a source of foodborne infection

Consumption of contaminated meat and poultry products is responsible for more than 40 percent of all bacterial foodborne illnesses in the United States each year.[3] Between 2005 and 2015, approximately 207 million pounds of meat and poultry products were recalled in the U.S. because of potential contamination with *Salmonella*, *Listeria monocytogenes*, or Shiga toxin-producing *E. coli*. While only a relatively small fraction of the meat produced in the U.S. is recalled each year, recalls due to these three pathogens represent close to half of all meat and poultry products recalled for any reason, including for contamination with other pathogens, chemical residues, allergens, and such. (See Figure 1.)

Figure 1

Recalls of Meat and Poultry by Product Type and Pathogen



Note: "Mixed meat" consists of meat from more than one species; "other meat" comes from species other than beef, pork, or poultry (e.g., sheep, buffalo).

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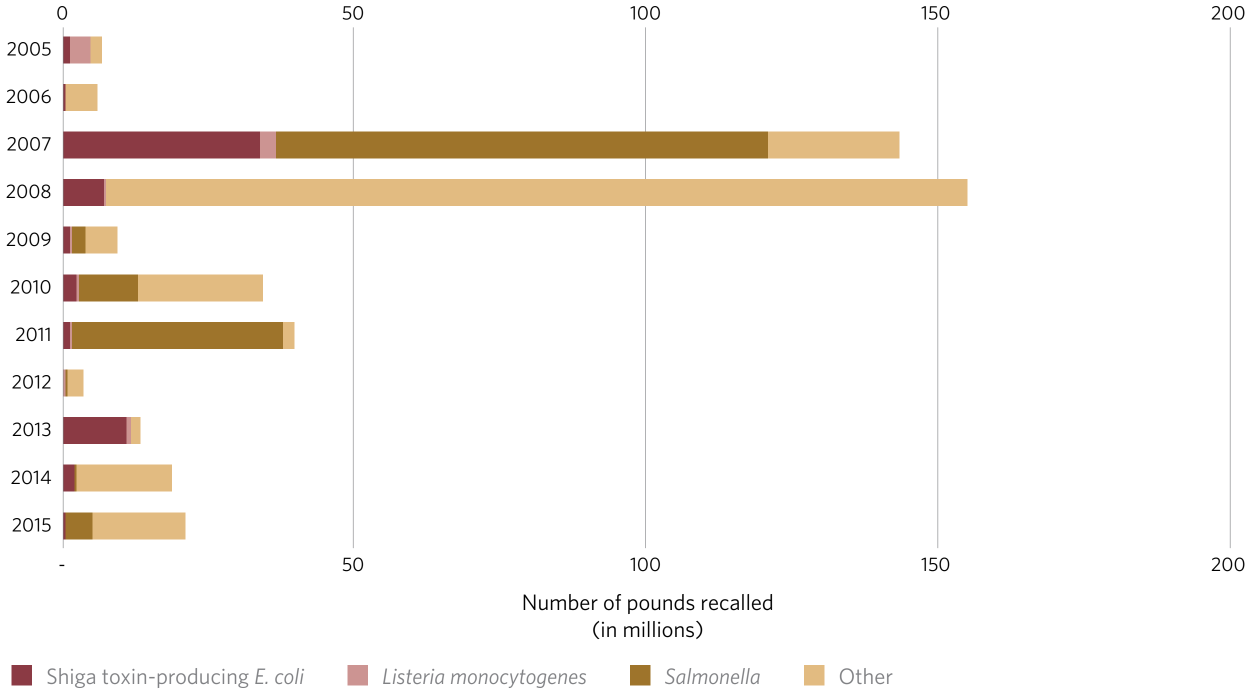


Source: Food Safety and Inspection Service, "Summary of Recall Cases," for years 2005-15, accessed Feb. 8, 2017, http://www.fsis.usda.gov/wps/portal/fsis/topics/recalls-and-public-health-alerts/recall-summaries/recall-summaries-2015

Globally, as many as half of all bacterial illnesses attributable to chicken consumption are caused by *Salmonella*, and *Campylobacter* infections account for more than 15 percent; *E. coli* and *Salmonella*, meanwhile, are the leading bacterial causes of beef-associated illnesses, and *Salmonella* is the primary cause of illnesses linked to pork.[4] Yet, numerous other microbial pathogens are also regularly transmitted to humans through meat or poultry consumption, including *Listeria monocytogenes*, *Yersinia enterocolitica*, and *Toxoplasma gondii*.[5] Efforts to estimate the relative contribution of different food vehicles to the burden of foodborne illness in the U.S. are ongoing and in general identify the same types of pathogens associated with meat and poultry consumption.[6]

In the U.S., the annual cost of illness due to consumption of meat and poultry products has been estimated at nearly $2.5 billion for poultry, $1.9 billion for pork, and $1.4 billion for beef.[7] These numbers include health-related expenses but do not account for the costs to government of outbreak investigations or for recall-related costs incurred by industry.

Although the food industry's actual costs related to food safety problems are generally not publicly available for a variety of reasons, including measurement difficulties and access to data, a 2011 survey of grocery manufacturers found that 77 percent of industry members polled who had experienced a recall within the preceding five years estimated the related costs at up to $30 million. Notably, 23 percent of respondents reported even higher costs, including 5 percent of respondents who estimated the cost at more than $100 million. Over 81 percent described the financial consequences of a recall as "significant" or "catastrophic."[8] Important recall-related costs captured in the survey include business disruption and lost profits, recall execution (such as product disposal and customer reimbursement), liability risks, and damage to reputation and brand equity.[9] In one case, the outbreak of *Salmonella* Heidelberg illnesses linked to Foster Farms chicken led to a 25 percent drop in company sales.[10]

Efficacy of pre-harvest interventions

This report focuses on pre-harvest interventions that can reduce contamination with foodborne pathogens in meat from cattle, swine, or poultry. Data for other meat-producing species is also relevant but exceedingly limited. Information on pre-harvest interventions that affect contamination of dairy or eggs is beyond the scope of this report.

Pre-harvest interventions are defined here as substances or management practices applied to farm animals to improve public health by reducing microbial contamination risks in the food products they generate. The interventions discussed can be grouped into three categories (see Appendix C for more information, including what is known about the mechanism of action as well as benefits and drawbacks of each intervention):

1. **Pro-commensal strategies** indirectly inhibit the pathogen by favoring competition with nonpathogenic bacteria. They include prebiotics, which are sugars and other organic compounds that are indigestible to humans and animals but that can be broken down by certain types of beneficial gut microbiota. They also include probiotics, live cultures of microorganisms added to the diet to improve intestinal microbial balance. Special types of probiotics are competitive exclusion products, bacterial cultures that are added to the intestinal tract of animals soon after birth to stave off pathogen propagation.
2. **Anti-pathogenic strategies** combat the pathogen, either through direct interaction with the pathogen or by priming the animal's immune response. They include:
   a. Vaccines, which aim to develop immunity comparable to that which develops after natural infection but without the negative impacts caused by the disease.
   b. Antimicrobial peptides such as bacteriocins and colicins, which are produced by bacteria and are toxic to foodborne pathogens.
   c. Bacteriophages, viruses that can infect and kill bacteria.
   d. Veterinary drugs, including antimicrobial drugs and sodium chlorate, a chemical compound that is toxic only for certain bacteria, such as *Salmonella* and *E. coli*, that possess the enzyme nitrate reductase.

   A variety of other products also apply anti-pathogenic strategies—including essential oils, heavy metals, and immune modulators—but data on their efficacy as pre-harvest interventions for food safety are so far insufficient to allow evaluation in this report.
3. **Exposure-reduction strategies** reduce the risk of pathogen introduction into or spread within the herd or flock. They include biosecurity, which includes measures such as access control, quarantine, and pest management to prevent introduction of infectious agents onto premises. They also include feed and water hygiene, management practices that reduce the opportunity that sick animals in the herd infect others, as well as adequate housing—measures that improve animal health, reduce stress, and minimize the risk of pathogen contamination.

Farm animal species differ in physiology and reproductive parameters. (See Table 1.) Not all pre-harvest interventions are effective or feasible for all animals, production systems, and pathogens. Some are simply incompatible with the physiology of certain species or pathogens. For example, prebiotics in ruminants are digested before they can be effective, and pre- and probiotics are ineffective against *Campylobacter*.

Other interventions are impractical to use in certain animal species or age groups. Animal production differs drastically among species. Beef cattle, for instance, are on average raised for about two years before slaughter, whereas the average broiler chicken lives only slightly more than a month. At the same time, a single broiler-breeder chicken will lay approximately 150 to 180 eggs, enough to produce more than 100 broiler chickens per year, whereas a beef cow will produce a single calf per year. (See Table 1.)

This has important implications for the feasibility and cost-effectiveness of various interventions for different species and for when, where, and how these interventions may best be used in the production chain. For example, applying certain pre-harvest interventions to broiler-breeder chicken to prevent infection in the offspring for the first few weeks of life and thereby reducing pathogens at slaughter may be feasible, effective, and cost-effective, given the short life span of broiler chicken and the large number of offspring per broiler-breeder chicken. By contrast, the same may not be feasible or effective for beef cattle.

In reality, pre-harvest interventions will likely have to be used in combination to achieve desired effects. However, limited peer-reviewed and published research has been conducted on the potential synergistic or antagonistic effects when different interventions are combined, and data on optimizing treatment regimens (timing of use, for instance) are scarce. Moreover, fragmentation of the supply chain may create disincentives because those that would have to bear the costs may not be able to realize any tangible benefits that occur downstream in the supply chain.

The amount of published research differs drastically among species, pathogens, and interventions. Considerably more research has been conducted on pre-harvest interventions for Shiga toxin-producing *E. coli* in beef cattle than for *Salmonella*. Large intervention trials are relatively scarce for pre-harvest interventions against *Salmonella* in swine and *Salmonella* and *Campylobacter* in poultry. In research on poultry, nearly all studies have focused on chicken, with very few available for turkeys. In general, there is a dearth of studies conducted under real-world conditions—on commercial operations, in the animals and age groups of concern.

Pre-harvest interventions need greater attention from all stakeholders and must be considered separately, depending on the species, age group, and production system.

Pre-Harvest Interventions and Antibiotic Use in Food Animals

Many of the pre-harvest interventions discussed in this report are also effective against bacteria that can make food animals sick but pose little or no health risk to people who consume meat from these animals. These interventions can reduce the need to use antibiotics to treat disease in food-producing animals.[11] Such nonfood safety benefits are beyond the scope of this report but are reviewed in a separate publication, "Alternatives to Antibiotics in Animal Agriculture," available at pewtrusts.org.

Table 1

Comparison of Key Production Parameters for Cattle, Swine, and Poultry

	Chicken	Turkeys	Cattle	Swine
Basic reproductive parameters				
Average gestation[a] period/ time to hatch	21 days[b]	28 days[c]	9 months[d]	16 weeks[e]
Time to weaning	n/a	n/a	6-8 months[f]	2-5 weeks[g]
Average weight at weaning	n/a	n/a	350-600 lbs.[h]	6-22 lbs.[i]
Breeding-related parameters				
Average offspring per litter[j]	1 egg/24-32 hours[k]	1 egg/24-32 hours[l]	1 calf	10 piglets[m]
Average litters per year	150-180 eggs/year[n]	100-130 eggs/year[o]	1 calving/year	2 litters/year[p]
Age at sexual maturity	24 weeks[q]	28 weeks[r]	14-15 months[s]	32 weeks[t]
Slaughter-related parameters				
Average age at slaughter	5-7 weeks[u]	12-14 weeks (hens)[v] 16-19 weeks (toms)[w]	18-24 months (though some are harvested earlier)[x]	22-26 weeks[y]
Average live weight at slaughter	5 lbs.[z]	14-20 lbs. (hens)[aa] 35-42 lbs. (toms)[bb]	900-1,400 lbs.[cc]	225-300 lbs.[dd]
Average time from breeding to slaughter	8 weeks[ee]	16-18 weeks (hens)[ff] 20-23 weeks (toms)[gg]	2.75 years[hh]	38-42 weeks[ii]

[a] For cattle and swine, this is the period between breeding and birthing of the litter. For poultry, this time is the period from egg fertilization to hatching.

[b] Melvin L. Hamre, "Hatching and Brooding Small Numbers of Chicks," University of Minnesota Extension (2013), http://www.extension.umn.edu/food/small-farms/livestock/poultry/hatching-and-brooding-small-numbers.

[c] Ibid.

[d] Thayer Watkins, "Gestation Periods and Animal Scale," San Jose University, accessed Sept. 26, 2016, http://www.sjsu.edu/faculty/watkins/gestation.htm.

[e] Ibid.

[f] Clay P. Mathis and Manny Encinias, "Early Weaning Beef Calves," New Mexico State University Cooperative Extension Service (August 2005), http://aces.nmsu.edu/pubs/_b/B126.pdf.

g Graeme Taylor and Greg Roese, "Basic Pig Husbandry—The Weaner," The Pig Site (April 18, 2006), http://www.thepigsite.com/articles/1616/basic-pig-husbandry-the-weaner.

h Gene J. Pirelli, Shirlee Weedman-Gunkel, and Dale W. Weber, "Beef Production for Small Farms: An Overview," Oregon State University Extension Service (January 2000), http://ir.library.oregonstate.edu/xmlui/bitstream/handle/1957/19237/ec1514.pdf; "Feeding Market Beef," Colorado State University Cooperative Extension and Department of Animal Sciences (n.d.), https://extension.unh.edu/resources/files/Resource002288_Rep3366.pdf; Pennsylvania State University Extension, "Beef Cow-Calf Production" (2013), http://extension.psu.edu/business/ag-alternatives/livestock/beef-and-dairy-cattle/beef-cow-calf-production.

i Steve Dritz, "Weaning Weight—Why It's More Important Than You Think," Kansas State University Agricultural Experiment Station and Cooperative Extension Service, *Swine Update* 20, no. 2 (1998), https://www.asi.k-state.edu/doc/swine-update/su0498.pdf.

j For chicken and turkeys, this is the average time to produce fertile eggs.

k Pennsylvania State University Extension, "Modern Meat Chicken Industry," accessed Sept. 26, 2016, http://extension.psu.edu/animals/poultry/topics/general-educational-material/the-chicken/modern-meat-chicken-industry.

l Pennsylvania State University Extension, "Modern Turkey Industry," accessed Sept. 26, 2016, http://extension.psu.edu/animals/poultry/topics/general-educational-material/the-chicken/modern-turkey-industry.

m U.S. Department of Agriculture, National Agricultural Statistics Service, "Overview of the United States Hog Industry," (October 2015), http://usda.mannlib.cornell.edu/usda/current/hogview/hogview-10-29-2015.pdf.

n Pennsylvania State University Extension, "Modern Meat Chicken Industry."

o Pennsylvania State University Extension, "Modern Turkey Industry."

p U.S. Department of Agriculture, Economic Research Service, "Hogs & Pork: Sector at a Glance," last modified June 27, 2017, https://www.ers.usda.gov/topics/animal-products/hogs-pork/sector-at-a-glance/.

q Pennsylvania State University Extension, "Modern Meat Chicken Industry."

r Pennsylvania State University Extension, "Modern Turkey Industry."

s Mississippi State University Extension, "Reproductive Management of Beef Cattle Herds" (n.d.), https://extension.msstate.edu/sites/default/files/publications/publications/p2615_0.pdf.

t U.S. Department of Agriculture, Economic Research Service, "Hogs & Pork: Sector at a Glance."

u Pennsylvania State University Extension, "Modern Meat Chicken Industry"; U.S. Department of Agriculture, Animal and Plant Health Inspection Service, "Poultry 2010: Structure of the U.S. Poultry Industry, 2010" (2011), https://www.aphis.usda.gov/animal_health/nahms/poultry/downloads/poultry10/Poultry10_dr_Structure.pdf.

v Pennsylvania State University Extension, "Modern Turkey Industry."

w Ibid.

x Pirelli, Weedman-Gunkel, and Weber, "Beef Production for Small Farms"; California Cattlemen's Association, "How Cattle Are Raised," accessed Sept. 9, 2016, http://www.calcattlemen.org/cattle_101/how_cattle_are_raised.aspx.

y U.S. Department of Agriculture, Economic Research Service, "Hogs & Pork: Sector at a Glance."

z Pennsylvania State University Extension, "Modern Meat Chicken Industry."

aa Pennsylvania State University Extension, "Modern Turkey Industry."

bb Ibid.

cc Pirelli, Weedman-Gunkel, and Weber, "Beef Production for Small Farms"; "Feeding Market Beef," Colorado State University Cooperative Extension and Department of Animal Sciences.

dd Washington State University, "Requirements for Fair," accessed Sept. 28, 2016, http://extension.wsu.edu/ferry/wp-content/uploads/sites/4/2016/07/Feeding-Tips-Market-Animals.Hog_.pdf.

ee Pennsylvania State University Extension, "Modern Meat Chicken Industry"; Hamre, "Hatching and Brooding Small Numbers of Chicks."

ff Pennsylvania State University Extension, "Modern Turkey Industry"; Hamre, "Hatching and Brooding Small Numbers of Chicks."

gg Ibid.

hh Watkins, "Gestation Period and Animal Scale"; Pirelli, Weedman-Gunkel, and Weber, "Beef Production for Small Farms."

ii Watkins, "Gestation Period and Animal Scale"; U.S. Department of Agriculture, Economic Research Service, "Hogs & Pork: Sector at a Glance."

Note: The parameters vary by an animal's genetic makeup, an operation's geographic region and size, and other factors, and animal productivity tends to increase over time. These data are meant to illustrate the considerable differences among the four species, and all source citations are provided; however, parameters found in other references may diverge from the information shown here.

Efficacy of pre-harvest interventions for poultry

Salmonella and *Campylobacter* are the primary pathogens of public health concern for poultry consumption that can be addressed through pre-harvest interventions. Notably, important differences exist in the epidemiology and infection sources for the two pathogens (see box, Page 12), as well as in their pathophysiology (that is, the disordered physiological processes that lead to disease). Therefore, an intervention's efficacy against one of the pathogens does not automatically indicate efficacy against the other. In fact, several pre-harvest interventions appear to be more effective against *Salmonella* than *Campylobacter*.

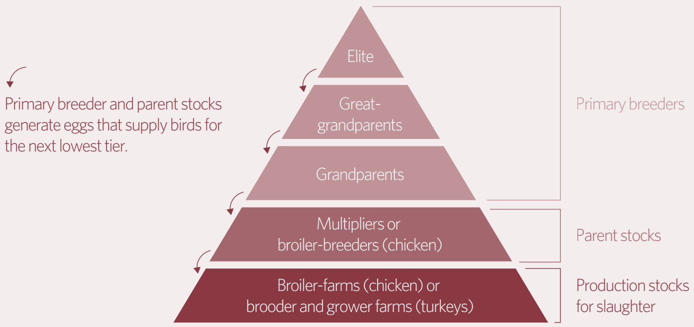
The Poultry Industry

For practical purposes, the U.S. poultry industry can be divided into broiler farms that raise chicken for meat, turkey farms that raise birds for meat, breeder farms that produce the birds for broiler or turkey farms, table egg farms that produce eggs for consumption, and farms that raise other poultry species such as ducks or geese.

Broiler farms make up the vast majority of poultry operations in the U.S., accounting for about 65 percent of farms in 2010, followed by turkey and breeder farms, which each accounted for roughly 15 percent of poultry farms.[12] (Table egg farms make up less than 3 percent of poultry farms and will not be discussed here.)

Figure 2

Poultry Industry Structure



Primary breeder and parent stocks generate eggs that supply birds for the next lowest tier.

Source: U.S. Department of Agriculture, Animal and Plant Health Inspection Service, "Highlights of Structure of the U.S. Poultry Industry, 2010," (November 2011), https://www.aphis.usda.gov/animal_health/nahms/poultry/downloads/poultry10/Poultry10_is_Structure_highlights.pdf.

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Poultry breeding flocks are organized in a pyramid structure, which enables intense genetic selection and allows genetic improvements to be disseminated quickly across flocks. At the top are small, highly selected elite flocks, which provide eggs that will hatch into the birds that will make up the great-grandparent flocks and provide eggs for the grandparent flocks. Grandparent flocks produce the eggs for the multiplier flocks, and eggs from multiplier flocks hatch into the production birds that will generate the poultry meat. In 2010, 89 percent of broiler-breeder farms were multiplier farms that produced production birds.[13]

Vertical integration is extremely common in the poultry sector, particularly among production flocks. Almost all broilers are raised by contract farms. Individual companies contract with the farmers and often own the multiplier flocks and hatcheries that produce the broiler birds, the slaughter facilities, and the feed used to raise the birds. In 2010, the median number of farms per broiler company equaled more than 460.[14] Only 58 percent of turkey-production farms, however, owned hatcheries, and the average number of farms per company was 141, indicating structural differences across the poultry sector.[15]

Most broiler farms are considerably larger than breeder and turkey farms. In 2010, 32 percent of broiler farms had more than 100,000 birds. Only 12 percent had less than 50,000 birds, compared to 99 percent of breeder farms and 73 percent of turkey farms.[16]

Production birds are typically placed into bird houses within a day of hatching (a process called placement), where they are allowed to roam around freely.[17] Broilers reach their market weight in about five to seven weeks,[18] whereas turkey hens require on average slightly more than 14 weeks and turkey toms require nearly 20 weeks.[19] At that point, catching teams will enter the bird house, manually catch the birds, and load them into shipping crates for transport to slaughter.[20] In some countries, particularly in Europe, production flocks are partially depopulated before reaching the final market weight, a process called thinning. Thinning optimizes space utilization and allows for production of more meat per square foot.[21] However, the process of catching a fraction of the flock leads to considerable stress for the birds, and the catching crew can introduce pathogens such as *Campylobacter*.[22]

Due to the pyramid flock structure, short production cycle from hatching to slaughter, and the large number of eggs laid per breeder bird (150-180 eggs per bird per year), multiplier flocks may be the most appropriate, feasible, and cost-effective place to target some pre-harvest interventions such as certain vaccines that can continue to afford protection to broiler chicken during grow-out. Vertical integration in the poultry sector facilitates interventions at early steps of the production chain because the multiplier flocks are often owned by the same company controlling all subsequent production steps through slaughter, as well as feed sources and downstream poultry processing operations.

Although the chicken and turkey industry are more similar to each other than to the swine or cattle sectors, important differences do exist, including a lower degree of vertical integration in the turkey industry, a longer time for turkeys between hatching and slaughter, and smaller average flock sizes compared to chicken. These differences have to be considered in the evaluation of pre-harvest food safety interventions, which have focused primarily on broiler chickens.

Sources of *Salmonella* and *Campylobacter* on Poultry Farms

Salmonella is a ubiquitous organism that can enter poultry houses from a variety of sources, including contaminated feed, water, litter, wildlife, farm personnel, and equipment. Because of potential vertical transmission or infection in the hatchery, contamination can also be introduced with the birds at the time of placement, emphasizing the need for efficient *Salmonella* control even at preceding steps of the poultry chain (for example, with the elite flocks, broiler-breeder flock and hatchery). The relative importance of different *Salmonella* sources is difficult to assess and likely to vary across production systems and housing types. Contaminated litter may be a particularly important source of *Salmonella* infection in broiler chicken and on carcasses,[23] at least under certain circumstances. Several studies have demonstrated that *Salmonella* contamination on commercial poultry farms can be relatively widespread.[24]

Salmonella control programs such as those in Sweden and Denmark have focused on three key aspects: production of *Salmonella*-free chicks for placement in broiler houses by eradicating the pathogen from breeding flocks and hatcheries; hygiene and management practices to ensure chicks are placed into *Salmonella*-free houses, such as an all-in/all-out system with thorough cleaning and disinfection of the house between flocks; and prevention of infection during rearing by controlling *Salmonella* in feed, water, and the bird house environment.[25]

The sources of *Campylobacter* infection in poultry flocks have received considerable attention.[26] Contrary to the situation for *Salmonella*, most scientists believe that vertical transmission from the breeder flock or hatchery plays a relatively minor role, if any, in *Campylobacter* epidemiology, although this point is still debated.[27] Broiler flocks are therefore typically regarded as *Campylobacter*-negative at the time of placement.

Campylobacter is considerably less stable in the environment than *Salmonella*, so sources such as feed are unlikely to be important vehicles for infections.[28] Therefore, farm biosecurity is thought to be the key determinant of whether a flock will become positive before slaughter.[29] Notably, age of the birds at slaughter was found to be positively correlated with the risk of conversion to a *Campylobacter*-positive status, as were season and management-related factors such as thinning. A meta-analysis of *Campylobacter* sources on broiler farms identified several specific risk factors, such as the presence of adjacent broiler or laying hen houses; insects including beetles, flies, and litterbugs; or rodents. The presence of hygiene barriers was found to have a protective effect. For numerous factors, such as different water sources, no statistically significant effect could be found.[30]

The vast majority of pre-harvest intervention studies have focused on broiler or broiler-breeder flocks. These results may or may not be transferable to turkeys; additional efficacy studies are needed. For chicken and turkeys and similar to the situation for other species, relatively few studies have been conducted on commercial operations under real-world conditions; more are needed.

These limitations notwithstanding, some interventions have shown very promising results. (See Appendix D for a detailed analysis of the literature on individual pre-harvest interventions for poultry, including pertinent citations to the scientific literature.)

For *Salmonella* control in chicken, interventions such as vaccination, prebiotics, and probiotics are promising and are already used commercially. Vaccination provides limited cross-protection against serotypes not included in the vaccine and commercial vaccines are available for only some *Salmonella* serotypes, but vaccination is a feasible option both in broiler and broiler-breeder flocks and can be an effective control strategy. Similarly, pre- and probiotics are highly promising interventions, in particular when added to the feed, and their efficacy is not limited to specific serotypes. Biosecurity and feed and water hygiene are also effective at reducing the risk of *Salmonella* introduction into the flock and should be considered as a basic requirement for raising chicken. Other feed- and water-related interventions, such as the addition of organic acids or the choice of heat-processed feed, may also reduce the *Salmonella* risk and should be considered.

Other interventions such as bacteriocins, bacteriophages, and sodium chlorate may ultimately also prove effective against *Salmonella* in chicken, but scientific studies have been limited and on occasion yielded variable or even seemingly contradictory results. Questions about feasibility also remain. For instance, the efficacy of bacteriophages is highly strain-specific and appears typically short-lived, so that phage cocktails of multiple strains will likely have to be used to ensure efficacy against a sufficiently broad range of *Salmonella* strains and to prevent the rapid emergence of resistant strains. As concluded by a formal European Food Safety Authority (EFSA) opinion on the subject, antimicrobial drugs are not generally recommended as pre-harvest interventions for *Salmonella* in chicken because of the associated risks, including the emergence of resistant strains and disruption of the bird's gut microbiome, which can ultimately increase the risk of pathogen shedding.

The landscape appears vastly different for *Campylobacter*. To date, biosecurity and improved management practices appear to be the most promising interventions for this pathogen. Bacteriophages have also shown promising results. Vaccination may be a feasible approach, but no vaccine is available commercially. Some other interventions such as bacteriocins may ultimately prove to be viable pre-harvest interventions for this pathogen, but realistic field trials are currently missing and technical challenges will have to be overcome before these interventions are ready to be applied in commercial settings, even for efficacy studies.

In fact, key questions remain about how *Campylobacter* is introduced into flocks. More basic research on these fundamental questions may prove valuable for determining effective pre-harvest interventions for this pathogen, which is particularly difficult to address. Other approaches, such as breeding animals with increased *Campylobacter* resistance, have been explored and may hold some promise.[31] Some important data gaps also continue to exist for *Salmonella*, including the mechanisms responsible for an observed correlation between food composition and shedding rates. More basic and applied research is needed to better understand the impact of external factors on the efficacy of pre-harvest interventions and to permit the development of administration protocols for pre-harvest interventions that are optimized for the conditions on a specific farm.

So, pre-harvest interventions are promising for *Salmonella* and, to a lesser extent, *Campylobacter* in chicken, although more research is needed for both. While international experts seem to agree about certain issues—for example, that antimicrobials are not recommended as pre-harvest interventions for poultry and that vaccination is a promising intervention to control at least certain *Salmonella* serotypes in chicken—many questions remain. *Campylobacter* in particular continues to pose immense scientific as well as logistical challenges and may require its own set of pre-harvest interventions.

Efficacy of pre-harvest interventions for cattle

Even though beef cattle may spend most of their lives grazing in pastures on cow-calf, stocker, and grower operations, feedlots are likely to be the most appropriate places to target pre-harvest interventions in cattle, for various reasons. This captures the time closest to slaughter. Most beef is derived from feedlot cattle, even though culled dairy cows and calves, veal, and cattle from other production systems contribute to the beef supply. The feedlot sector is less fragmented than cow-calf operations, and a sizable fraction of the beef supply is provided by a few very large feedlots. Interventions may be more logistically feasible on feedlots than on expansive pastures. The risk of infection on feedlots may also be higher, given the stress associated with movement and mixing of animals, the high concentration of animals from different sources, and the change from low- to high-energy feed.

The Cattle Industry

The U.S. cattle industry has undergone substantial changes—albeit more modest than in the pork and poultry sectors—with a clear trend toward fewer, larger operations. Over the past two decades, the average number of cattle per operation in the U.S. has increased by 36 percent (although numbers have recently begun decreasing again),[32] while the number of operations has decreased by 28 percent.[33] Dairy beef from culled dairy cows and dairy calves contributes an estimated 18 percent of the beef supply.[34] The rest is provided by beef cattle, including veal (calves), steers (castrated male cattle), heifers (young females before their first calving), and culled beef cows.

Nearly all beef cattle in the United States are born on cow-calf operations, where cows typically remain on pasture year-round and calves are weaned at six to eight months when they weigh roughly 400 to 600 pounds.[35] "Seedstock" producers are specialized cow-calf operations that maintain and improve purebred and hybrid genetic lines.[36] "Commercial" cow-calf operations that produce cattle raised for beef production can purchase animals (particularly breeding bulls) from seedstock producers or other herds. Alternatively, they often retain some of their female offspring as replacement animals.[37]

Beef cows on cow-calf operations are fed primarily through grazing and supplementation (for instance, minerals and proteins), with no or limited quantities of grain. The resulting considerable land requirements tend to limit herd sizes in cow-calf operations, and that sector remains highly fragmented. In fact, income from these operations is a supplemental source in many cases. Small-scale operations with fewer than 50 beef cows are not uncommon.[38]

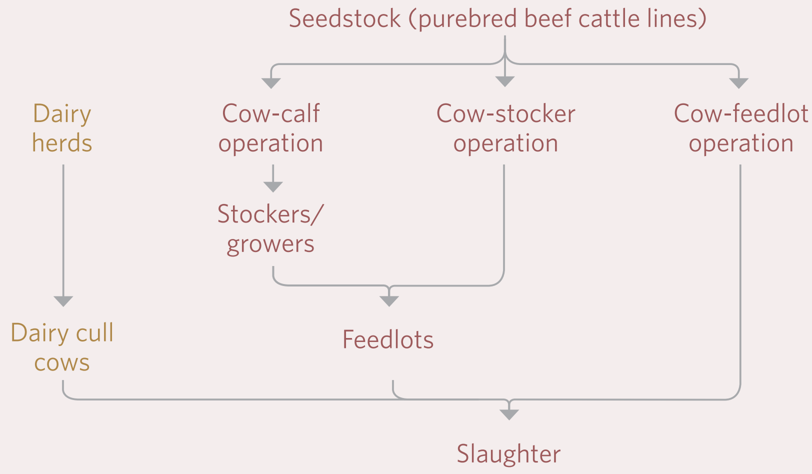
Continued on next page

Many beef calves are sold as feeder calves soon after weaning, even though some operations retain weaned calves to be raised as replacement animals or to be fattened for a limited time before being sold to feedlots or directly to slaughter.[39] (See Figure 3.) Feeder calves are often sold to stocker operations, where they will continue to be fed on feeds with relatively low energy density (that is, pasture or roughage).[40] At some point, typically when weighing about 800 pounds, most beef cattle will be placed on commercial feedlots for finishing (the final phase of the production process where animals are fed to reach final market weight, at which time they will be slaughtered). There, cattle will be housed in pens[41] and fed high-energy feed, primarily grain and protein concentrates, which allows for considerably higher stocking densities and increased daily gains. This allows cattle to reach market weights of more than 1,000 pounds by 18 to 24 months of age, even though some cattle are marketed at a younger age.[42]

Contrary to cow-calf operations, economies of scale are easily realized in feedlots. The number of very large feedlots with capacities of 32,000 cattle or more increased by more than 50 percent between 1996 and 2011, while the number of small feedlots with 1,000 cattle or fewer decreased by 32 percent during the same time period.[43] In fact, by 2011, more than 40 percent of all feedlot beef cattle in the U.S. were found on large feedlots and only 18 percent on small ones, even though operations with more than 1,000 cattle capacity made up less than 5 percent of all feedlots.[44] A very small number of very large feedlots thus provide most of the beef cattle to slaughter operations.

Figure 3

Cattle Industry Structure



Breeding heifers can come from seedstock or can be retained from animals bred by an operation.

Unlike in the poultry and swine sectors, implementing pre-harvest interventions in breeding herds is not feasible in the cattle sector because of the longer time between birth and harvest and because the cattle industry does not have the pyramid structure of tightly controlled breeding herds typical of the poultry and swine sectors. Most studies of pre-harvest interventions in cattle have focused on *Salmonella* and Shiga toxin-producing *E. coli*, the leading public health concerns associated with beef. Some pre-harvest interventions may also be effective for other pathogens, but experimental data are so far scarce.

Most beef produced in the U.S. is derived from feedlot cattle that are housed on very large feedlot operations, fed a high-energy diet and slaughtered 18 to 24 months after birth. Yet, only a few studies of pre-harvest interventions have been conducted on commercial feedlots. (See Appendix E for a review of the available data.) Data collected in dairy cattle or feedlot cattle housed on small experimental farms may inform the efficacy of pre-harvest interventions on feedlots, but differences in management, housing, and other husbandry practices complicate this extrapolation. Data collected on calves are even more challenging to interpret, given the vast physiological, immunological, and management changes calves undergo as they mature. To date, most pre-harvest interventions for cattle have been evaluated only for *E. coli* O157:H7 and, to a lesser extent, *Salmonella*. Pre-harvest interventions may vary in efficacy by pathogen, and the relevance of *E. coli* O157:H7 data for other foodborne pathogens is difficult to determine. In addition, many relevant scientific questions have so far remained unanswered, including why certain feeds seem to increase *E. coli* O157:H7 shedding, the mechanism of action for probiotics, and the productivity gain observed after experimental vaccination against *Salmonella* but not *E. coli* O157:H7. (See Appendix E.)

Nonetheless, the efficacy of certain pre-harvest interventions is reasonably clear. For example, vaccination has been shown in many trials to effectively reduce the shedding of *E. coli* O157:H7. One adequate vaccine is available on the market, though a lack of economic incentives may hinder implementation. Another promising vaccine, which was licensed in multiple countries but not the U.S., was discontinued. It is also apparent that prebiotics are not effective for beef cattle, although advances in the delivery mechanism may change this in the future.

For two other commercially available pre-harvest interventions in cattle, the picture is significantly more complicated. Data are highly variable for vaccination against *Salmonella* and for the use of probiotics. A number of studies strongly suggest that, under the right circumstances, these interventions may lead to a significant decrease in fecal shedding and thereby effectively reduce the risk to the consumer. Yet, more field trials are needed to understand under which conditions these interventions may or may not be effective, what role external factors such as diet or season may play, what impacts these interventions may have on productivity and overall herd health, and how these interventions may best be leveraged. Technological advances such as the development of safe and dependable vaccines that generate cellular as well as humoral immunity, or of probiotics with bacteriocin-producing microorganisms, may lead to more effective products in the future, but advances in scientific research as well as regulatory challenges will have to be overcome first.

The practical value of other pre-harvest interventions is currently not clear. Sodium chlorate, for instance, has shown promising results in small-scale studies, but large field trials on commercial feedlots are missing. Without regulatory approval, widespread use will also not be possible. Bacteriophages have shown promising results in some studies and are available as hide sprays during harvest, but data on oral applications, which are the most feasible on large feedlots, are lacking. Some data suggest that these interventions may be useful only for a short time because of rapidly developing resistance, emphasizing that optimized timing may be crucial for efficacy. Data on the efficacy of antimicrobial drugs have been mixed. For several antimicrobials, pre-harvest administrations did not have a significant impact on fecal shedding or carcass contamination, but the therapeutic use of neomycin sulfate shortly before slaughter has been effective, at least under experimental conditions.

However, this application carries considerable risks, including those of drug residues and antimicrobial resistance development, which have to be prudently weighed against the potential benefits.

Most of the pre-harvest interventions probably are not very effective if used in isolation. Bacterial resistance can develop quickly, as demonstrated by the fact that individual bacteriophages or colicins are of limited and potentially short-lived usefulness. Combinations of interventions that address a variety of molecular targets are likely to be the most effective. In addition, basic factors such as biosecurity, feed and water hygiene, and adequate housing are prerequisites for animal health and, without them, no pre-harvest intervention will likely ever be truly effective. In the end, a thorough understanding of the scientific principles underlying pre-harvest food safety challenges in cattle and of the interventions designed to minimize the risk will be instrumental.

So, pre-harvest interventions are promising for controlling Shiga toxin-producing *E. coli* and, to a somewhat lesser extent, *Salmonella* in cattle. While cattle industry structure and the animals' physiology complicate implementing these, and while more data are needed, some pre-harvest interventions are already used successfully in commercial operations.

Efficacy of pre-harvest interventions for swine

Salmonella is the major pathogen of food safety concern for the swine industry, and nearly all pre-harvest intervention studies have focused on it. Contrary to the situation in the cattle industry, no specific point in the pig production chain can be identified where pre-harvest interventions should best be targeted, even though finishing barns may resemble feedlots in some respects. Controlling *Salmonella* infection in breeding herds has been identified as a first step in controlling *Salmonella* in high-prevalence pig herds.[45] This may be easier to achieve than in production herds given the pyramid structure of breeding herds, the relatively short period between farrowing and slaughter (six to seven months, compared with the 18- to 24-month average for cattle), and the unique challenges posed by increasing specialization and growing numbers of production contracts in commercial herds.

However, if *Salmonella* contamination is introduced at any point in the production chain from breeder to finishing herds, asymptomatically infected animals can carry it further. Stress, particularly during transport and lairage, can induce shedding and lead to widespread infections, potentially obliviating any pre-harvest effects achieved upstream.[46] The complete pig production chain is therefore relevant for pre-harvest interventions, making pork safety exceedingly complex. Nonetheless, pre-harvest control measures have been instrumental parts of national *Salmonella* control programs in countries such as Finland, Norway, and Sweden, which continue to lead the way on *Salmonella* control.[47]

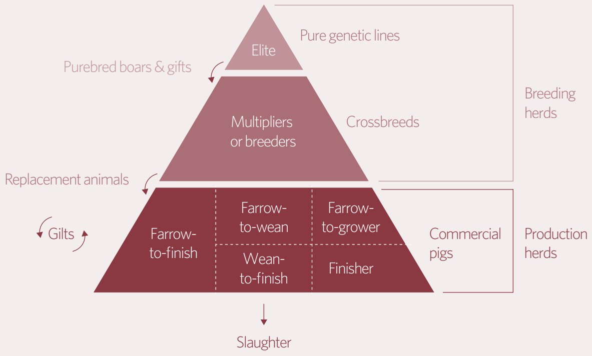
The Swine Industry

Market hogs (swine raised for meat) are typically derived from highly selected breeding stock.[48] Genetic improvements have led to leaner pigs that achieve improved daily gains, reach market weight more quickly, and have a higher average number of offspring per litter.

Swine breeding herds are organized in a pyramid structure. (See Figure 4.) At the top of the pyramid are elite or nucleus herds. These small and tightly controlled herds consist of purebred lines, are subject to intense genetic selection, and are controlled by a small number of companies.[49] Elite herds supply multiplier herds, which usually consist of crossbred animals. Multiplier herds provide boars or their semen to commercial pig herds, as well as replacement gilts (that is, females before birthing their first litter), even though gilts born in commercial herds may also be retained as replacement gilts.

The U.S. swine industry has undergone fundamental structural changes in the past decades with substantial increases in specialization and vertical integration and a trend toward larger operations.[50] Between 1992 and 2004, the number of U.S. hog farms decreased by more than 70 percent while the average number of hogs per operation more than quadrupled, from 945 in 1992 to 4,646 in 2004.[51] By 2004, upwards of 50 percent of hogs were located on operations with 5,000 hogs or more.[52] At the same time, hog production became increasingly specialized. Traditional farrow-to-finish operations that raise hogs from birth to slaughter have largely been replaced by those that specialize in a single phase of production, and a substantial fraction is now organized under production contracts.[53] Under these contracts, owners or "integrators" retain ownership throughout the hog's life but engage producers to raise the animals in a fee-for-service type of agreement. Production contracts specify the relationship between integrators and producers, and often spell out specific details related to feeding, veterinary care, and housing.[54]

Figure 4
Pork Industry Structure



Purebred boars and gilts are passed from the elite herds to the multipliers and breeders, replacement animals are passed from the multipliers and breeders to commercial pigs, and gilts from production herds can be retained for breeding.

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Pigs in commercial herds that produce market hogs are typically housed indoors in barns or outdoors on pastures, and in rare cases in semi-intensive units that combine indoor and outdoor facilities.[55] After approximately 114 days of gestation,[56] sows will birth a litter of approximately 10 pigs[57] (farrowing). To protect the litter from accidentally being crushed or otherwise harmed, sows are separated for farrowing (if otherwise housed together), placed into specialized pens or stalls, and typically remain there until the pigs are weaned at two to five weeks of age, when the piglets weigh about 10 to 15 pounds.[58]

The fate of the weaned pigs depends on the production system, even though integrated systems typically include separate barns or structures for different age groups. There are two predominant production types in the U.S., regardless of ownership structure: multi-site all-in/all-out and the less common continuous flow farms.[59] Currently, there are five major market hog production types in the U.S.:[60]

1. **Farrow-to-finish**, where pigs are farrowed and weaned, and remain on the farm until they reach market weight of 225 to 300 pounds.
2. **Farrow-to-feeder**, where piglets are farrowed, weaned, and raised until they weigh approximately 30 to 80 pounds and then leave the operation as feeders.
3. **Farrow-to-wean**, where piglets are farrowed and leave the operation immediately after weaning.
4. **Feeder-to-finish**, where feeder pigs are obtained and fattened until they reach market weight.
5. **Wean-to-feeder**, where piglets are obtained immediately after weaning and raised until they reach the feeder state, at approximately 30 to 80 pounds.

The picture of pre-harvest interventions in the swine sector is different from that for poultry and cattle. This is due, in part, to physiology—for example, a shorter period from birth to slaughter and absence of a rumen; industry structure, such as pyramid-shaped breeding herds and increasing specialization; and pathogens of key concern. In general, fewer research studies have been performed on pre-harvest interventions in swine than in cattle or poultry. Efforts to aggregate data in systematic reviews and meta-analyses are further limited by heterogeneous effects and variable and potentially suboptimal study design and reporting.

For vaccination, there is currently sufficient scientific evidence to support efficacy, at least under the right circumstances, even if cost-effectiveness has remained less clear. Similarly, there is general consensus against the routine use of antimicrobial drugs as pre-harvest interventions in swine. For most other pre-harvest interventions, there are currently only limited, or in some cases seemingly contradictory, efficacy data available. Pre- and probiotics, for instance, have been evaluated primarily for their growth-promoting effects, with highly promising results. These products may also be effective pre-harvest interventions, but studies have reported variable efficacy and more research is needed, including basic research to better understand their mechanism of action and the reasons for the highly variable efficacy. Sodium chlorate, bacteriophages, and bacteriocins have also shown promising results under experimental conditions, but more studies in real-world settings are needed, and some of the products have so far been evaluated primarily for their impact on animal health rather than as pre-harvest food safety interventions. Biosecurity and feed and water hygiene should be considered as a prerequisite for raising pigs. As with poultry and cattle, the choice of feed type may affect the risk of *Salmonella* shedding. Acidification of feed or water may also reduce the *Salmonella* risk, but data are less clear than for poultry and more research is needed.

In general, more studies are needed across the board to evaluate the efficacy and cost-effectiveness of pre-harvest interventions in swine, particularly in commercial market hog herds under realistic conditions. Results from *Salmonella* control programs in Europe demonstrate that pre-harvest interventions can be an option for reducing the risk of pork-attributable salmonellosis cases even though most impactful interventions were found to be at harvest and post-harvest stages. However, such programs will likely have to span the complete production chain, from breeding to finishing herds; consider the risk of cross-contamination and infection during transport, lairage, and slaughter; and include biosecurity, feed hygiene, and *Salmonella* testing and monitoring as well as specific pre-harvest interventions. Success will require considerable commitments of resources; the potential cost-effectiveness of pre-harvest interventions for swine is still actively debated by many experts.

Sources of *Salmonella* Contamination in Swine Herds

Understanding the sources of *Salmonella* contamination in swine herds is central to the effective implementation of pre-harvest interventions. In 1999, Stärk et al.[61] conducted an expert elicitation workshop to better characterize *Salmonella* transmission dynamics on pig farms and during subsequent transport and lairage. Several potential sources for *Salmonella* infection on pig farms were identified, including live pigs (such as replacement pigs from breeding herds), feed, people on the farm, and rodents, although experts differed in their assessment of the relative importance of these risk factors. The authors suggested that differences in opinion may have been caused, in part, by differences in swine industry structures in the experts' countries of origin. Unfortunately, the ubiquitous nature of *Salmonella* and its risk factors make intervention in these systems difficult.

A 2006 Opinion of the Scientific Panel on Biological Hazards of the European Food Safety Authority[62] (EFSA) concluded that infected pigs are the main source of *Salmonella* infection in swine production and central to the introduction of *Salmonella* into new facilities. Other identified sources included the environment and other animals that were infected, such as rodents or wildlife.

A risk assessment commissioned by EFSA and published in 2010 identified infected breeder pig herds, contaminated feed, and contamination from external sources such as rodents and birds as key sources of infection in their model. Notably, the relative contribution of these sources differed by *Salmonella* prevalence in the modeled countries, indicating that the primary infection source may differ by country and operation, depending on their *Salmonella* status.[63]

Roadblocks to implementation

In the United States, multiple federal agencies have authority over aspects of meat and poultry production, including approval of certain on-farm interventions such as vaccines or animal drugs. However, no one agency has clear authority to require the use of a particular intervention or to set on-farm standards that limit bacterial contamination. This regulatory landscape complicates the implementation of pre-harvest interventions and emphasizes the need for close alignment among and collaboration by industry and agencies that have authority over animal health and food safety-related issues.

Other roadblocks to implementation include the lack of economic incentive (particularly in highly fragmented industry segments), limitations in scientific knowledge and data, logistical challenges (such as facility characteristics, technological challenges, labor force), the ubiquitous nature of some of the pathogens, and physiological factors that may interfere with the efficacy of interventions for certain applications.

Numerous differences among the animal species and the industry structures are also relevant to implementation. The cattle industry has remained largely fragmented, whereas vertical integration is extremely common in the pork and poultry sectors. This has important implications for the economic feasibility of pre-harvest interventions.[64] In addition, the pathogens of major concern for pre-harvest interventions are not the same for all animal species,[65] and, due to their mode of action, many pre-harvest interventions are effective only for certain pathogens. Therefore considerations have to be made in the context of the animal species and production system in which they will be applied. Interactions with testing and monitoring programs also have to be considered. (See Appendix G.)

Recommendations

To improve food safety in the U.S. through pre-harvest interventions, Pew makes the following recommendations:

To funding agencies such as USDA's National Institute of Food and Agriculture

1. Extend funding opportunities to support:
   a. Relevant research, particularly into biosecurity and best management practices, which are foundational to pre-harvest food safety and effective across a wide variety of species, production systems, and pathogens but to date have not been a focus of most scientific research.
   b. Large field trials on commercial operations for interventions that may be promising but currently lack efficacy data, particularly for hard-to-address issues such as *Campylobacter* in poultry and swine and *Salmonella* in swine.
   c. Research on commercial operations to optimize application protocols, such as timing vaccination to maximize efficacy and cost-effectiveness.
2. Study the basic science, mechanism of action, ancillary benefits, and potential unintended consequences associated with poorly understood yet promising interventions such as pre- and probiotics, including alternative approaches that may reduce the need for antibiotics. Similarly, studies should also evaluate the cost-effectiveness of promising pre-harvest interventions as this will be a critical prerequisite for successful implementation.

3. Designate more funding to evaluate potential synergistic or antagonistic effects among interventions, the underlying drivers of variability in efficacy across farms and operations, and the cost-effectiveness of interventions, including potential incentives to increase uptake of the interventions by producers.
4. Consider incentives to spur research and development in the pre-harvest food safety area by providing, for instance, more grants and fostering public-private partnerships.

To federal agencies

1. Provide incentives for the implementation of pre-harvest food safety interventions, be they regulatory or economically motivated. In particular, consider strategies that lead to improvements in biosecurity and management practices as part of these incentives.
2. Expand the use of innovative tools such as risk assessments to systematically synthesize pertinent data and prioritize when and where interventions should be applied.
3. Improve the regulatory approval processes in such a way that product safety, consistency, efficacy, and quality can be guaranteed while making sure promising products can reach the market in a timely fashion. In particular, consider the value of technological advancements such as whole-genome sequencing for overcoming traditional challenges to regulatory approval.
4. Improve collaboration and communication among all stakeholders (farmers, meat producers, consumers, regulatory agencies, academic researchers, the pharmaceutical industry) to increase the availability and use of promising interventions. In particular, strengthen interagency collaborations to leverage technical expertise across and within organizations and closely align animal health and food safety responsibilities, even if they rest within different entities such as USDA's Food Safety and Inspection Service and Animal and Plant Health Inspection Service.

To industry

1. Emphasize the use of individual pre-harvest interventions as one part of a herd health management program, in the context in which they will be used (for example, animal species and age group, production system), along with potential synergisms or antagonisms between interventions. Evaluate whether ancillary benefits may be achieved, such as improvements in overall animal health that may reduce treatment costs and animal losses.
2. Provide adequate biosecurity, feed and water safety, and basic animal health standards as a prerequisite for the production of meat and poultry on farms and feedlots, even if biosecurity may be more challenging to ensure in some production systems (such as pasture-based systems) than others.
3. For industries in which a small number of breeding herds or flocks give rise to the production animals, consider the feasibility and potential value of pathogen eradication programs upstream, in elite herds or flocks, and create incentives for such programs where feasible.

To all stakeholders

1. Encourage data sharing among industry, academia, government researchers, and regulatory agencies to allow data on the efficacy and safety of these products from all settings to be used to the greatest extent possible. Public-private partnerships may be the most feasible approach to closing some of the data gaps that currently hinder the development and use of pre-harvest interventions. This will require overcoming legal and logistical challenges such as privacy and transparency concerns and IT infrastructure compatibility.

Conclusion

Pre-harvest food safety interventions can have a positive impact on public health, as the successes in several countries clearly show. However, the road to success is challenging. Even in countries that have achieved a zero or very low prevalence of *Salmonella*, success was neither cheap nor easy. It would not have been possible without the collaboration and buy-in among all stakeholders, the lasting commitment to sometimes costly and painful actions such as the depopulation of pathogen-positive flocks, and the continuing measurement and tracking of success.

The success stories and the available scientific data demonstrate the need for an integrated approach that relies on multiple components, not just one isolated intervention. This combination of approaches allows synergisms among the interventions to be utilized. It also reduces the likelihood that pathogens will quickly evolve to counteract the new intervention.

Biosecurity is a key prerequisite for on-farm food safety and may in fact be one of the few effective and currently feasible options for controlling *Campylobacter*. Feed and water safety are basic requirements for raising healthy animals, as are issues such as housing or ventilation that can increase or reduce stress and affect overall susceptibility to infection.

With the exception of biosecurity and feed and water safety, no single pre-harvest intervention is currently effective and feasible for all animal species, pathogens, and production systems. However, this does not mean that pre-harvest food safety is not possible. Interventions must be tailored to the targeted animal species, pathogen, and production system, and applied at the most effective time and in the best manner for the given situation, be that immediately before slaughter or before the animal is even born.

Some interventions are clearly promising, such as cattle vaccines against *E. coli* O157:H7 and potentially *Salmonella*, pre- and probiotics to reduce *Salmonella* in poultry, biosecurity to reduce the risk of *Campylobacter* infection in broiler flocks, and *Salmonella* vaccines in poultry and swine. Some farms and feedlots are already using pre-harvest interventions, even though cost-effectiveness questions remain for many of these interventions. In some cases technological advances may be necessary before promising interventions can be used in commercial settings.

Overall, pre-harvest interventions may be most effective, feasible, easy to implement, and promising for poultry, given the short production cycle, the pyramid structure of breeding flocks, and the observed efficacy of several interventions, at least for *Salmonella*. However, that does not mean that pre-harvest interventions are not an option for cattle or swine. In fact, numerous interventions appear highly effective against Shiga toxin-producing *E. coli* in cattle, and several interventions also generated promising results for *Salmonella*. Although efficacy and cost-effectiveness may be less clear for pre-harvest interventions in swine, in many cases more data are needed. There is certainly reason to be optimistic that some interventions, such as sodium chlorate, may ultimately prove to be attractive pre-harvest interventions in swine.

While few options (such as prebiotics and competitive exclusion products for cattle and antimicrobials for pigs and poultry) are clearly not effective or recommended pre-harvest interventions, at least given the current state of science and technology, for many interventions efficacy is not yet clear. The reasons include an overall dearth of large field trials on commercial operations, conflicting results in experimental studies, limited understanding of the external factors affecting efficacy, and low quality of individual studies that precludes meta-analyses and systematic evaluations. Cost-effectiveness, feasibility, and regulatory challenges are often also unclear. Additional pre-harvest interventions may be able to make significant strides in improving food safety, but data to date have been scarce and therefore may have simply not been able to demonstrate this potential.

Glossary

Adjuvant. A substance (such as aluminum hydroxide or paraffin oil) added to a (killed) vaccine to enhance the body's immune response to the vaccine.

All-in/all-out system. An animal husbandry practice in which all animals are of the same age, arrive at the same time, and leave for slaughter at the same time; this also allows for thorough cleaning of the enclosure between groups of animals.

Average daily gain. The rate of weight gain per day, measured over a specified period; a performance measure commonly monitored by animal producers.

Bacterial load. The quantity of bacteria present on an animal, food, or other object.

Bacteriophage. Virus that infects bacteria and can inactivate them.

Beef cattle. Cattle raised for the primary purpose of meat production.

Breeding herd or flock. A herd or flock that produces animals that will be raised for meat production.

Broiler. A chicken raised for meat.

Broiler-breeder. A bird in the breeding flock that generates the broilers for production flocks.

Carrier. An animal that harbors a pathogen and can spread it to other animals; carriers may themselves not show any signs of infection.

Catching teams. People who enter bird houses to catch birds and place them in crates for transportation to slaughter.

Competitive exclusion product. A type of probiotic, given soon after birth or hatching, that helps the animal establish beneficial bacteria in the gut before pathogens can colonize there.

Cow-calf operation. An operation that maintains a breeding cow herd; cows are usually kept on pastures throughout the year, and calves are allowed to stay with the mother cows for several months.

Dairy beef. Beef from dairy cows (slaughtered once they are culled from the dairy herd).

DIVA/marker vaccine. A type of vaccine that allows diagnostic tests to distinguish between vaccinated and naturally infected animals; DIVA stands for differentiating infected from vaccinated animals.

Elite/nucleus herds. Small, tightly controlled pig herds with intense breeding to improve production characteristics (such as daily gains, fertility); all market hogs can ultimately be traced back to elite herds.

Evisceration. The process of removing the internal organs from a carcass during slaughter.

Farrowing. The process of giving birth to a litter of pigs.

Feeder. The life stage of a production animal from shortly after weaning to finishing; this is typically an extended period of sustained growth.

Feedlot. A place in which cattle are fed to reach market weight before slaughter.

Field trial. A study design in experimental epidemiology in which an intervention (such as a product or production practice) is administered to part of a population at risk of contracting a disease (e.g., some cattle in a commercial feedlot or broilers on a commercial broiler farm) and disease outcomes (such as infection, mortality) are compared between those with and without the intervention to evaluate efficacy.

Finishing. The final life stage of a production animal, from feeder to slaughter, in which animals reach their market weight.

Gilts. Female pigs before their first litter.

Grandparent flock. The equivalent, for poultry, of elite herds.

Hatchery. An enterprise that artificially controls the hatching environment of eggs for commercial purposes to reduce losses and improve the health of the chick; commercial poultry typically hatches in hatcheries.

Heifers. Female cows before their first calving.

Horizontal transmission. The transmission of a pathogen within a herd or flock through direct contact between animals or indirect contact (for example, through environmental contamination).

Host range. The range of species a pathogen can infect.

Humoral immunity. The part of the immune system that is mediated by antibodies (as opposed to the cellular immunity, which is mediated through the interaction of immune cells with the pathogen).

Hygiene barrier. A physical barrier that limits the spread of environmental contamination by enforcing hygienic measures, for example, foot baths for farm staff.

Incidence. A measure of disease frequency, expressed as the number of new cases within a specified period (not counting cases with disease onset before the period of interest).

Integrators. Animal owners that retain ownership throughout the animal's life; producers raise animals for integrators under production contracts.

Lairage. The resting of animals after transport to the slaughterhouse but before slaughter.

Logistic slaughter. The process of scheduling slaughter based on flock or herd status, so that pathogen-positive herds are slaughtered last, thus minimizing the risk of cross-contamination from positive to negative flocks or herds during slaughter.

Market hog. Pig raised for meat.

Meta-analysis. A systematic statistical procedure of combining and synthesizing results from multiple research studies.

Pathogenicity. The ability of an organism to cause disease; many microorganisms contain pathogenic and nonpathogenic species (for example, *E. coli*).

Phage cocktail. A mixture of multiple bacteriophage strains.

Placement. The process of placing animals such as day-old chicks into bird houses; in that case, chicks are typically hatched in hatcheries and transported to the poultry farm for placement.

Prevalence. A measure of disease frequency expressed as the number of cases during a specified period, including those cases with disease onset before the specified interval.

Production animals. The animals raised for meat (in contrast to breeding animals that generate the production animals).

Production contracts. The legal agreements between integrators and producers that specify the terms according to which producers raise animals for integrators.

Prophylactic use. The use of antibiotics or other interventions to prevent illness.

Rumen. The first chamber of the alimentary tract of cattle, sheep, goats, and other ruminants.

Serology. The diagnosis of infection based on the detection of specific immune responses to a pathogen.

Sows. Female pigs that have birthed at least one litter.

Steers. Castrated male cattle raised for meat.

Therapeutic use. The use of antibiotics or other interventions to treat a disease.

Vertical integration. A management structure, common in the pig and poultry industries, in which multiple stages of the production chain (for example, breeding flocks, hatcheries, poultry farms, slaughter operations) are controlled by the same owner.

Vertical transmission. Transmission of pathogens from parent to offspring.

Water additive. A substance added to drinking water for a specific purpose.

Zoonotic infection. An infectious disease that can be transmitted between animals and humans.

Appendix A: Methodology

Methodology for literature review

Literature searches were conducted in the PubMed, Google Scholar, and Google search engines, supplemented by reviews of bibliographies in the identified literature. A publicly available database of meta-analyses in veterinary medicine[66] was reviewed in 2016 to identify additional meta-analyses relevant to pre-harvest food safety. The literature review was restricted to articles published in English.

When evaluating the efficacy, feasibility, or safety of interventions, results from systematic reviews and meta-analyses of randomized controlled trials were used whenever possible because they methodically and critically summarize several independent studies and are expected to constitute the strongest level of scientific support.[67] However, such studies are not available for all species, pathogens, and interventions. Because of the significant time commitment required to conduct such studies, published systematic reviews may not always reflect the most current scientific findings. Therefore, other literature reviews and original research articles were also considered in the report as appropriate. The report also benefited from expert opinions on pre-harvest interventions. Pew organized meetings and individual semistructured interviews to discuss the most current scientific evidence with renowned professionals in the area of pre-harvest food safety.

Methodology for expert workshops

Pew hosted a series of consultations with experts in cattle and poultry and conducted semistructured discussions with the expert panels during the workshops. For cattle, a one-day meeting with five experts (one participated via phone) was held at Pew's offices. WebEx was used for the other meeting due to scheduling issues and the project's time constraints. Two experts participated in the WebEx. A draft version of this report (pre-peer review) was sent to all experts before the workshop. The goal of the meetings was to provide appropriate context for the efficacy of different pre-harvest interventions in swine or poultry. Specifically, the workshop provided an opportunity to discuss the existing scientific evidence and research needs, and to receive overall feedback on the report. A draft of the report, including a draft of the workshop summaries, was shared with the experts for review after the meeting. Due to scheduling conflicts, a workshop on swine could not be organized. The recommendations and conclusions from recent EFSA opinions on pre-harvest interventions for swine were substituted for the workshop because they met similar goals as those that guided the workshops for cattle and poultry.

Table A-1

Summary of Semistructured Discussion From the Cattle Workshop

Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Prebiotics	-	-	-	Easy to administer Likely wide consumer acceptance	Limited/no usefulness in ruminating animals due to degradation in the rumen Potentially high economic cost Potential for niche alteration	Substances to prevent breakdown during rumen passage Impact on environmental shedding Ability to verify adoption
Probiotics: Competitive exclusion	-	+++	+	Short-lived animal health impacts in calves possible Easy to administer Likely wide consumer acceptance Likely impact on environmental shedding	Limited impact on food safety Time between administration and harvest too long in ruminants for treatment to remain effective Microbial changes during rumen development limit usefulness Potential for niche alteration	Mechanism of action Efficacy in calves Ability to verify adoption

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Probiotics: Direct-fed microbials	++	+++	++	For some products consistent reduction in prevalence and concentration of *E. coli* O157:H7 demonstrated at higher probiotic doses (in beef cattle) One commercial product currently widely used in feedlots Easy to implement on large feedlots; potential practical limitations in certain other settings Relatively low economic cost Likely wide consumer acceptance Impact on environmental shedding	No FDA drug approval (i.e., no label claims or potency information) GRAS approval No specific good management practices (GMPs), quality assurance/ quality control (QA/QC), validation No specific assays (e.g., for determination of dose, strain composition, viability) Difficult to verify adoption Potential for niche alteration Efficacy highly variable across products and strains	Mechanism of action Evaluation of efficacy (currently only available for few probiotics) Efficacy in dairy cows and calves (data currently focused on feedlot cattle) Efficacy for pathogens other than *E. coli* O157:H7

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Vaccines	++	+++	++	Impacts on animal health and production as well as food safety Demonstrated efficacy for *E. coli* O157:H7; efficacy correlated with number of administered doses; some commercial products on the market, others in pipeline Some efficacy for reduction of *Salmonella* fecal shedding Easy to implement on feedlots; efficacy may differ across production settings Adoption easy to verify Likely more widely acceptable to consumers than some interventions, even though vaccination may be unacceptable to some consumers Impact on environmental shedding	Protection relatively serotype-specific Heterogeneity of effect (depending on measured outcome, sample matrix, number of doses) Some limitations in availability (e.g., conditional licensing) Potential negative impacts on animal performance (e.g., production loss) Potentially high economic cost Potential for immune selection for non-cross-reactive strains Efficacy differs across pathogens	Efficacy for other pathogens and serotypes (e.g., *Salmonella* serotypes) Efficacy for other outcomes than fecal shedding (e.g., lymph node colonization) Data to evaluate time-period effects Mechanisms underlying potential negative effects of vaccination on animal performance (e.g., stress-related impacts, direct vaccine effects) and differences across vaccines

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Sodium chlorate	+++	+	-	Promising results in reducing fecal loads of a broad spectrum of pathogens in small-scale studies No negative impact on biological population of the rumen/intestine Low toxicity Easy to administer (if given as top-dress)	No market approval Useful primarily at very specific points around harvest, and primarily for certain high-stress situations Not tested systematically; no field data available Potentially limited consumer acceptance Potential for chemical side effects (e.g., chemical exposure, corrosion) Limited to no impact on environmental shedding	Use under realistic field conditions (currently small-scale experimental studies only) Potential for development of resistance Correlation between reduction in fecal load and contamination of hides Efficacy if used in dairy cows Economic cost; mass-quantity chemical of low economic cost but some potential for price increase after FDA approval and potential patent protection Ability to verify adoption depending on potential assay development during FDA approval process
Bacteriocins and colicins	-	-	-	Potentially more useful if administering probiotic strains that generate these bacteriocins (limited data on efficacy available) Easy to administer	Production in large quantities challenging Degradation in rumen (shielding from degradation possible but challenging) No delivery mechanism ready to market Potentially high economic cost Potentially less acceptable to consumers than some other interventions Potential for niche alteration Efficacy in ruminating cows unclear	Data on efficacy in ruminating cows Ability to verify adoption Impact on environmental shedding

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Antimicrobial drugs (e.g., neomycin, ceftiofur)	+++	+++	++	Therapeutic use 2-3 days pre-harvest (with 1-day withdrawal) through medicated feed or water has proved efficacious in feedlot settings against *E. coli* O157:H7 Field-trial efficacy data available Easy to administer Easy to verify adoption	Potential problems associated with use of antimicrobials include selection for highly resistant strains, risk of drug residues, potential risk of environmental accumulation and exposure Inconsistent efficacy at lower doses and for other products, pathogens, and strains Potentially high economic cost Potentially limited consumer acceptance Limited impact on environmental shedding	

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Bacteriophages	+	+	++	Fairly widely used seasonally as hide-spray Relatively low economic cost if administered to hide; potentially higher if administered in diet Easy to verify adoption if administered to hide; less clear for administration through diet	Potential evolution of the phage Potential for selection of resistant bacterial strains and transmission of microbial resistance or virulence genes among bacterial hosts (primarily of concern for use in diet) May require continuous dosing Efficacy may be specific to certain pathogens and strains Efficacy may differ between hide-spray and oral administration Potentially challenging to implement (e.g., labor intensive, implementation potentially dependent upon seasonal and climatic factors) Potentially limited consumer acceptance Limited to no impact on environmental shedding Data on efficacy (i.e., reductions in prevalence and concentration) very limited	Methodology to clearly prove efficacy (current analytical limitation) Differences between use under laboratory conditions and on live animals complicate extrapolation of data More efficacy data Data on evaluating efficacy for dairy cows Cost of administration through diet

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Diet and water treatment	Prerequisite (i.e., a necessary condition for raising healthy animals)			Feed and water are potential vehicles for pathogens, but the impact of stricter hygiene standards is difficult to evaluate; may differ by pathogen, overall pathogen status of the operation, etc. Inclusion of brewer's yeast consistently and reproducibly increases risk of shedding for certain pathogens when compared to corn-based diets Shedding rates may differ by crop type (e.g., barley, corn, cotton) and/or forage quality	Use as interventions currently not clear, will likely require understanding of the mode of action or at least more experimental data	Mechanism of action Data for several types of grains and different pathogens
Biosecurity	Prerequisite			Wildlife (e.g., birds) have been shown to shed *E. coli* O157:H7 and other pathogens such as *Campylobacter* Control of wildlife populations has been shown to have some impact Evidence for the correlation between environmental conditions (e.g., pen maintenance) and shedding rates in feedlots	Limited experimental studies demonstrating direct impact on pathogen prevalence and/or concentration Yet, FSIS and industry guidelines for pre-harvest pathogen controls identify interventions that, even in the absence of a demonstrated impact on prevalence, are certainly beneficial (e.g., clean feed and water; self-draining environment; pest and insect control)	Effect may differ by setting; efficacy not always clearly demonstrated in experimental studies Differential impacts across geographic regions, pathogens, management practices

[a] Effective product/product formulation ready for use

Table A-2

Summary of the Semistructured Discussion From the Poultry Workshop

Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Prebiotics	++	++	++	Yeast-cell products are promising for *Salmonella* Thought to stimulate immune system Have been shown to help control different pathogens Numerous products on the market Used in breeders during raising phase and in broilers Easy to administer with feed Relatively cheap Reasonably large amount of scientific evidence available	Cannot control all microbial issues in flock Not promising for *Campylobacter*	Mechanisms of action Not a lot of work in recent years

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Probiotics: Competitive exclusion	+++	+++	+	Potentially effective against *Salmonella* Easy to implement, especially in feed; water a bit more complicated	Not currently used in poultry Limited products with FDA approval Too expensive to be feasible Only efficacious if given very early Complex to produce and ship Not effective against *Campylobacter* Affects bacterial load shed more than prevalence Can interfere with live vaccines Can increase biofilm in waterline especially if sugar carrier; may not have practical impacts on intervention choices, though Moderate to high cost	More research has been focused on application in broilers than broiler-breeders Impact of various external variables on efficacy Quantitative reduction in *Salmonella* shedding for a given situation (e.g., bird age, season, *Salmonella* strain) Effectiveness across serotypes and subtypes (e.g., individual *S.* Typhimurium strains)

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Undefined direct-fed probiotic	+++	+++	-	Effective against *Salmonella* Most effective probiotics Combination of multiple bacterial species most effective Easy to implement, especially in feed; water a bit more complicated Considerable research available on efficacy	No FDA approval route because lacking definition of strains; none currently approved as drug Not effective against *Campylobacter* Cannot be given in ovo (embryo will not hatch) Affects bacterial load shed more than prevalence Can increase biofilm in waterline (especially if sugar carrier); may not have practical impacts on intervention choices, though Potential risk for antimicrobial resistance transfer Moderate cost	Composition of bacterial strains Potential variability in mode of action across products and bacterial strains Differences among strains of bacterial species Differences in efficacy across farm locations and with time Interactions with the microflora in the poultry's gut Impact of changes in feed (e.g., starter feed to grower feed) Quantitative reduction in *Salmonella* shedding for a given situation (e.g., bird age, season, *Salmonella* strain) Effectiveness across serotypes and subtypes (e.g., individual *S.* Typhimurium strains)

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Defined direct-fed probiotic	+++	+++	+++	Effective against *Salmonella* Heat-stable probiotics (e.g., spore formers, *B. subtilis*, *B. licheniformis*) can be given with pelleted feed, easier to administer, seem to have better efficacy Less effective than undefined probiotics Products on market Administration through feed most promising Easy to implement, especially in feed; water a bit more complicated Considerable research available on efficacy	Non-heat-stable probiotics have to be added through water Water additives can be difficult to give (e.g., dosing, water quality, and waterline system, not compatible with water disinfectants) Administration as mist in hatchery complicated (e.g., interactions with vaccinations) Not effective against *Campylobacter* Can be given in ovo but administration to reach the gut variable and possibly difficult to control Affects bacterial load shed more than prevalence (reduce *Salmonella* spreading through the flock) Can increase biofilm in waterline (especially if sugar carrier); may not have practical impacts on intervention choices Moderate cost	Variability in mode of action Differences among strains Genetic determinants of specific strain characteristics Differences in efficacy across locations and time Interactions with the microflora in the poultry's gut Impact of changes in feed (e.g., starter feed to grower feed) Quantitative reduction in *Salmonella* shedding for a given situation (e.g., bird age, season, *Salmonella* strain) Effectiveness across serotypes and subtypes (e.g., individual *S.* Typhimurium strains)

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Vaccines: Live vaccines	+++	+++	+++	Effective for controlling *Salmonella* Vaccination of broiler-breeders shown to affect *Salmonella* load in processing plant Consistently effective Some cross-protection against multiple serotypes Used in broiler-breeders Vaccines on the market Reduces bacterial load on carcasses Generates maternal antibodies for *Salmonella* Relatively easy to administer (e.g., water, spray) Limited interference with serology Considerable research available on effectiveness	Limited cross-protection against other *Salmonella* serotypes No long-term protection; may need to readminister or combine with inactivated vaccine Vaccines can be expensive; may be too expensive for routine use in broilers No vaccines available for *Campylobacter*	Field studies in actual facilities Case-control studies in real-world settings Vaccine trials for *Campylobacter*

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Vaccines: Inactivated vaccines	+++	+++	+++	Effective for controlling *Salmonella* Vaccination of broiler-breeders shown to affect *Salmonella* load in processing plant Used in broiler-breeders Consistently effective Longer-term protection than live vaccines Reduce bacterial load on carcasses Commercial products for *S. enteritidis* and one for multiple strains with some cross-reactivity Most inactivated vaccines currently used are autogenous Generates maternal antibodies for *Salmonella* Easy to implement, though labor-intensive Considerable research available on efficacy	No or limited cross-protection against multiple serotypes Not economical in broilers Autogenous vaccines have no information on efficacy (due to regulatory limitations) No vaccines available for *Campylobacter* Endotoxins can cause depression and effects on feed consumption Humoral immune response can create serological cross-reactivity (e.g., false-positive results for *S.* Gallinarum-Pullorum, potential surveillance program issues in the U.S. and other serological surveillance systems) Vaccine and labor can be expensive Not used in broilers	Field studies in actual facilities Case-control studies in real-world settings Vaccine trials for *Campylobacter* Efficacy in broilers

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Sodium chlorate	+++	+	-	Effective against facultative anaerobic bacteria (e.g., *Salmonella*, *E. coli*, *Clostridium*) Can act synergistically with probiotic Likely administration in hatchery and right before harvest, or throughout the rearing process Residue profile not different than if given sodium chloride solution Easy to implement, especially in feed; water a bit more complicated Compound is cheap	Not commercially available Causes wet litter if concentration is too high (increases water uptake with diet) Affected by water (e.g., NaCl concentration in water), not as easily taken up through feed as water Limited data available on efficacy under field conditions Very scarce data in breeders No effect on *Campylobacter*	Field studies under real-world conditions
Bacteriocins and colicins	+	+	-	Efficacious in laboratory studies	Not used in real-world conditions No commercial product on market Limited scientific data available Cost of implementation currently not clear	Experimental studies under commercial conditions

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Bacteriophages	+	+	-	Efficacious in laboratory setting Used in water under experimental conditions Can be used for other pathogens than *Salmonella (Campylobacter)*	Not used on farms Do not work consistently Commercial product used for processing plants (spray treatment) Very serotype-specific or even specific to individual strains within a serotype (i.e., isogenic phages) Will not survive pelleting process for feed Difficult to administer Commercial cost currently unclear Limited data available in the English literature	Experimental studies under commercial conditions

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Organic acids in water	++	++	+++	Effective in high-load situations Replaces acid generated by *Lactobacillus* during feed withdrawal prior to harvest Used during first and last week of life Works primarily in crop; limited impact in caecum (because of buffering capacity of intestine) but some potential impact on caecal load Reduce colonization of crop, which is primarily caused by coprophagia Easy to administer (but need to get concentration right; high pH can affect efficacy) Reasonable body of scientific evidence available on efficacy	Not routinely used by most farmers Not used as much in breeders as in broilers (may be used in feed for breeders in the future) Palatability issues if used in higher concentration; potential weight loss going into the slaughterhouse Potential damage to equipment (e.g., medicators) Cheap (if administered through water); feed-based organic acids not yet well understood and cost not clear	Experimental studies under commercial conditions
Water disinfection (e.g., chlorination)	++	+++	+++	Continuous application to chlorinate water from nonmunicipal sources Works very well against *Campylobacter* Relatively easy to administer but some limitations (e.g., dose, mixing, pH) Relatively cheap Considerable amount of scientific data available	Substitute for municipal water source Potential for equipment damage (depends on factors such as water hardness)	

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Pre-harvest intervention	Biological efficacy	Strength of scientific evidence	Market readiness[a]	Summary of		
				Benefits/use	Barriers/limitations	Data gaps/future research needs
Essential oils (e.g., oregano)	+	+	++	Some antibacterial efficacy Promising against *Clostridium* and *Salmonella* Products on the market	Limited scientific data available Potentially less effective in the field than in experimental studies Not very well understood Cost of implementation currently not clear Data on efficacy among breeders very scarce	Experimental and field studies under commercial conditions Experimental studies in breeders Ease of application depends on heat stability and formulation; real-world use fairly unclear
Biosecurity	+++	++	++	One of the only things that can be effective for *Campylobacter* Very important for *Salmonella* as well	Can be difficult to implement Implementation expensive	

[a] Effective product/product formulation ready for use.

Appendix B: The role of pre-harvest interventions in the U.S. food chain

Salmonella, *E. coli*, *L. monocytogenes*, *Campylobacter*, and a number of other important foodborne pathogens are zoonotic, or capable of infecting humans as well as animals. Various scientific studies have repeatedly shown that these pathogens are present on U.S. farms and feedlots, sometimes at a high frequency and in very high concentrations.[68] In many cases, infected animals do not exhibit any symptoms of infection, even while they shed pathogens in their bodily fluids.[69] The presence of foodborne pathogens on farms or feedlots is a risk factor for the contamination of meat, poultry products, and other foods and therefore poses a public health risk.[70] Yet, a variety of factors determine if pathogens will indeed lead to contamination, from the pathogen and animal species involved to various pre-harvest, harvest, and post-harvest management practices that can increase or decrease the risk.[71]

Contamination Pathways for Foodborne Pathogens

In addition to contamination of meat and poultry products, the presence of pathogens on the farm can also pose a public health threat in other ways, such as for farm staff and visitors who come into direct contact with pathogens.[72] Pathogens from the farm can enter the surrounding environment in the water, soil, and air. People may be directly exposed to such environmental contamination, or indirectly through consumption of contaminated produce grown in this environment. These transmission routes are important to consider but inherently difficult to study and quantify; many aspects of these risks remain unknown.[73] Nonfoodborne risks are beyond the scope of this report.

Pathogens can be introduced into the farm or feedlot environment in numerous ways, including through animal feed, water, livestock, wildlife, pets, vermin, farm staff, farm equipment, and visitors. Many pathogens of concern can survive in the farm environment for days, weeks, or even months.[74] Therefore, barns, stables, pastures, and other areas of the farm or feedlot can serve as a pathogen reservoir and may be a source of infection, even if they have not housed animals for some time.[75]

The prevalence of some foodborne pathogens on farms appears to differ by season.[76] Climatic factors can affect pathogen survival in the environment or the susceptibility of animals to infection, and can therefore affect how a pathogen enters and spreads within a herd or flock. Most pathogens survive longer in cool, wet environments rather than dry.[77] Ultraviolet radiation in sunlight has been shown to inactivate pathogens.[78] Notably, hot weather can increase stress for the animals,[79] and stress in general increases susceptibility to infection.[80] At the same time, crowding of animals during cold weather can increase contact rates and may favor the transmission of pathogens in a herd or flock.[81]

Management-related factors can also affect susceptibility to foodborne pathogens and thereby food safety.[82] Adequate diet and housing play major roles in ensuring animal health.[83] Poor ventilation, for instance, can lead to respiratory diseases and increase stress.[84] Certain housing types that increase the contact animals have with manure may favor the transmission of foodborne pathogens.[85]

Young animals are more susceptible to infection than adult animals.[86] Management systems where all animals are of roughly the same age, such as all-in/all-out systems, may therefore lead to different pathogen transmission dynamics in herds than systems that combine different age groups, where older animals may represent a source of infection for younger animals.[87] All-in/all-out systems can provide certain biosecurity benefits, especially if facilities are thoroughly cleaned and sanitized between herds or flocks.[88] Commingling age groups and/or herds can lead to injuries and intense stress as social structures are re-established; systems that avoid such mixing can be preferable.

How animals are loaded and transported from the premises to slaughter, and how they are housed in the slaughterhouse, also can have major impacts on food safety.[89] While these factors are not strictly part of pre-harvest interventions, they can have clear implications for farm biosecurity and the effectiveness of pre-harvest interventions.

Pre-harvest interventions can improve meat and poultry safety in various ways. Procommensal strategies (probiotics, for example) affect the ability of the pathogen to colonize the animal; anti-pathogenic strategies combat the pathogen, either by directly interacting with the pathogen (bacteriophages, bacteriocins, and colicins) or by priming the animal's immune response to a specific pathogen (such as vaccination); and exposure-reduction strategies (such as biosecurity, feed and water hygiene) reduce the risk of pathogen introduction into the herd or flock.[90]

The importance of harvest and post-harvest interventions

Typically, foodborne pathogens are restricted to the gastrointestinal tract of live animals and, to a lesser extent, the draining lymph nodes; the muscle tissues that will yield the vast majority of the meat or poultry products are free of pathogens.[91] The slaughter process provides numerous opportunities for the muscle tissues to become contaminated. Sources include fecal contamination on surfaces or equipment, leakage of intestinal content (and crop content in birds) during evisceration, contact with contaminated hides or feathers, and contaminated lymph nodes.

Due to the significant risk of carcass contamination during slaughter, a variety of harvest and post-harvest interventions have been designed to minimize the risk. These interventions include management-related factors such as optimizing feed withdrawals prior to slaughter to minimize the risk of fecal contamination and intestinal leakage,[92] and the implementation of logistic slaughter processes in which animals from herds or flocks known to be pathogen-positive are slaughtered last.[93] Other relevant interventions include bagging and tying the bung (rectum), and removing particularly highly contaminated carcass parts such as neck skin or hoofs.[94] A variety of technological interventions can be applied during or after slaughter to reduce microbial contamination on carcasses, including water washes, chemical treatments such as chlorine washes, or steam.[95]

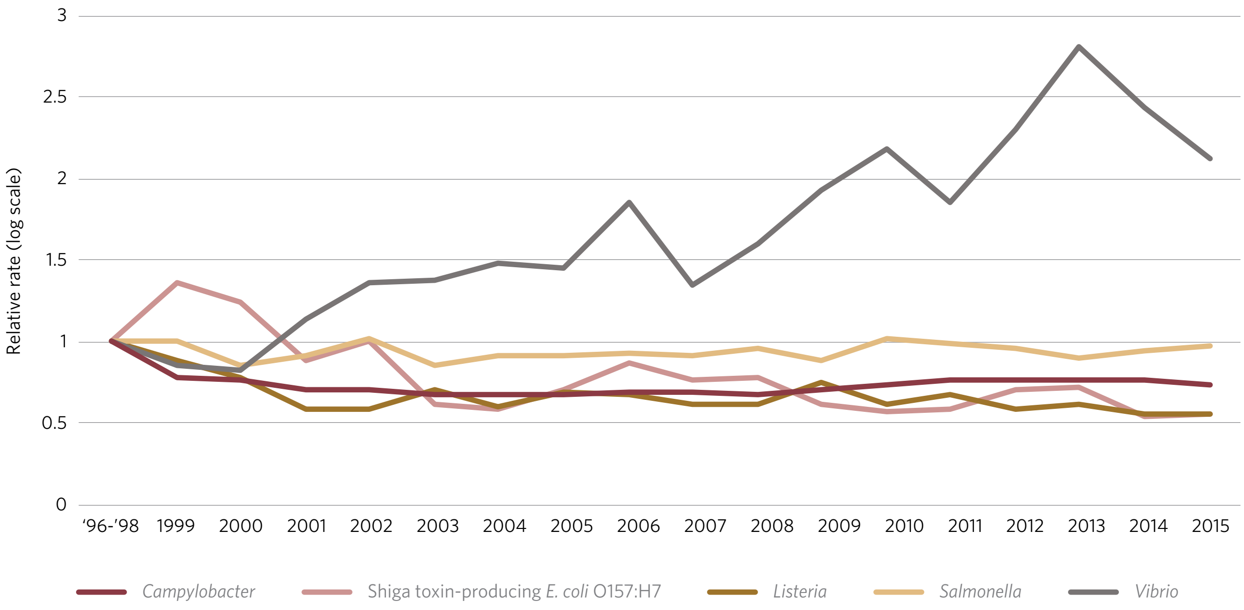
Impact of Post-Harvest Interventions on Public Health

The meat and poultry industry and government agencies have enacted strategies to control pathogens and reduce contamination during the slaughter and processing stages. Prevention-based regulations known as the Pathogen Reduction/Hazard Analysis and Critical Control Point (PR/HACCP) were put in place for facilities that slaughter or process meat or poultry.[96] PR/HACCP requires each facility to develop a written food safety plan, conduct active management and monitoring of microbial and chemical hazards identified in the plan, and make records available to government inspectors upon request.[97]

Industry responded by adopting a series of post-harvest measures such as carcass rinses and steam vacuum systems and processing improvements such as temperature control. This led to a significant reduction in human infections from *E. coli* O157:H7. However, in recent years, little progress has been made in reducing infections linked to pathogens such as *Salmonella* and *Campylobacter* (see Figure B-1), and in some cases, rates of infection remain roughly unchanged.[98]

Figure B-1

Relative Rates of Culture-Confirmed Infections Compared With 1996-98 Rates, by Year



Source: Centers for Disease Control and Prevention, Foodborne Diseases Active Surveillance Network (FoodNet), “FoodNet 2014 Annual Foodborne Illness Surveillance Report,” last modified April 18, 2016 , http://www.cdc.gov/foodnet/reports/annual-reports-2014.html

Appendix C: Mechanism of action for selected pre-harvest interventions

Pre-harvest interventions fall into three broad categories:[99]

1. **Procommensal strategies,** such as prebiotics and probiotics, which indirectly inhibit the pathogen by favoring competition with nonpathogenic bacteria.
2. **Anti-pathogenic strategies,** such as bacteriocins, bacteriophages, and vaccines, which directly target the pathogen.
3. **Exposure-reduction strategies,** which minimize the risk of pathogen introduction on the premises. Many of these strategies—including adequate housing, feed and water hygiene, and management practices—also improve overall animal health, help eliminate stress, and reduce the susceptibility of animals to pathogens that may be present on the premises.

Pre-Harvest Interventions Typically Target One of Three Pathogens

Pre-harvest interventions have primarily focused on three bacterial pathogens: *Salmonella*, *Campylobacter*, and *E. coli* O157:H7. Other pathogens are of pre-harvest concern and some interventions may also be effective against some of these other pathogens, but efficacy data are typically scarce or lacking altogether.

Salmonella

Salmonella is a foodborne bacterial pathogen that can infect a very broad range of animal species, including mammals, birds, reptiles, amphibians, fish, and insects.[100] Many asymptomatically infected animals only shed the bacterium intermittently, primarily when stressed, which complicates the detection of *Salmonella* carriers.[101] *Salmonella* remains viable in the environment for long periods, and infection through inanimate objects has been identified as a key contributing factor in outbreaks.[102] *Salmonella* infection typically occurs through ingestion of food or water contaminated with manure, although it can also be present in many tissues that can serve as a source of infection such as gallbladders, lymph nodes, and tonsils.[103] *Salmonella* colonizes the intestinal epithelium in specific parts of the gastrointestinal tract: the ileum and, less commonly, the jejunum, duodenum, and stomach.[104] This colonization makes certain pre-harvest interventions such as prebiotic approaches (based on bacterial competition for the space to colonize the necessary areas) viable.

Currently, more than 2,500 *Salmonella* serotypes are recognized, which differ drastically in host range, in the clinical disease they cause, and in the foods they are primarily associated with.[105] Prior exposure through previous infection or vaccination with a different serotype provides some cross-protection, but the amount depends on the serotypes involved.[106]

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Infections of most *Salmonella* serotypes are primarily asymptomatic in livestock species and typically do not cause large economic losses on farms or feedlots, but they do pose a food safety risk.[107] Notable exceptions are serotypes Gallinarum and Pullorum, which cause severe economic losses in poultry operations but do not pose a food safety risk because they do not infect humans.[108] Mandatory eradication programs have been successful at removing these two serotypes from commercial U.S. poultry flocks.[109]

Pathogenic *E. coli*

Cattle are the primary reservoir for pathogenic *E. coli* such as *E. coli* O157:H7 or other Shiga toxin-producing *E. coli*.[110] Pathogenic *E. coli* have been found in other species such as pigs or chicken, but at very low incidence.[111] *E. coli* is therefore primarily a pre-harvest concern for beef.

E. coli infection occurs through the fecal-oral route.[112] Similar to *Salmonella*, Shiga toxin-producing *E. coli* colonizes the intestinal epithelium through a number of specific molecular interactions that may present targets for pre-harvest interventions.[113] Wildlife does not generally constitute an important reservoir for pathogenic *E. coli*, but it can survive in the environment for long periods, and in some cases, such as in contaminated manure, can multiply.[114]

Notably, the incidence of pathogenic *E. coli* in very young calves appears to be considerably lower than in older animals, such as older calves and heifers.[115] Transmission among cattle, directly or through contact with contaminated environments, is believed to be the major transmission route on cattle operations.[116]

Campylobacter

Campylobacter can infect a variety of meat-producing species including cattle, pigs, and poultry, but infection often remains subclinical and outbreaks of foodborne illness are almost exclusively limited to raw milk or poultry consumption.[117] Infections in animals are often asymptomatic but can be severe in humans.[118]

The exact molecular mechanism by which *Campylobacter* attaches to epithelial cells in the intestine during colonization remains unclear,[119] along with how exactly *Campylobacter* colonizes broiler chicken flocks.[120] Whether vertical transmission (from the parent flock) is possible is subject to debate, even though the relative contribution of this pathway, if it exists, is generally believed to be fairly minor.[121] More important transmission pathways are thought to be other animals (like wild birds or livestock) and vehicles such as contaminated water, insects (flies, beetles), or human transmission from farmworkers and visitors.[122]

Procommensal strategies

Commensals, in this context, are nonpathogenic bacteria that live in the gut of humans or animals and benefit from the environment (nutrients, for example) but do not exert any negative impacts on the human or animal they colonize. Procommensal strategies work by favoring the establishment of a beneficial nonpathogenic microbial microflora in the gut that prevents foodborne pathogens from colonization.[123] Once the beneficial microflora has been established, all ecological niches in the gut will have been filled and pathogens will not readily find niches that can be exploited for colonization.[124] The beneficial microflora can be established by directly including beneficial bacteria (probiotics) in the diet or by including substances such as sugars or other organic compounds (prebiotics) that will be selectively utilized by the beneficial microflora and will confer them with a competitive advantage.[125]

Probiotics

Probiotics or direct-fed microbials are live cultures of microorganisms added to the diet to improve intestinal microbial balance.[126] The beneficial microorganisms can be of a specific bacterial species, such as the lactic bacteria included in yogurt, or may be mixtures of bacteria, fungi, and yeasts.[127] Defined probiotics consist of individual strains or mixtures of microorganisms comprehensively described to the species level and with the exact composition of the culture; genomes of individual organisms may also have been fully sequenced. Undefined probiotics tend to consist of mixtures of microorganisms that are not completely described.[128]

Probiotics provide resistance against gut colonization by pathogens and exclude pathogens through competition, even though the exact molecular mechanisms have largely remained open to scientific debate.[129] A variety of additional effects have been ascribed to specific probiotic strains, even though these effects are likely strain-specific and include reinforcement of the gut barrier, immunological effects, and direct pathogen antagonism.[130] In animals, probiotics have been used to prevent animal diseases such as post-weaning diarrhea in pigs, reduce the shedding of foodborne pathogens such as *E. coli* O157:H7, and improve production characteristics such as average daily gains, milk yield, or feed efficiency.[131] Certain segments of the animal industry, in particular the cattle sector, are widely using probiotics.[132] Notably, probiotic bacteria can carry and transmit antibiotic-resistance genes, emphasizing the need for careful characterization of probiotic cultures.[133]

Competitive exclusion is a specific form of probiotic in which a bacterial culture is added to the intestinal tract of food animals very shortly after birth to stave off pathogen propagation.[134] The gastrointestinal tract of neonatal animals is largely sterile initially but will quickly be colonized, most commonly by microbiota from the mothers or environmental sources.[135] Pathogens can establish themselves during these early stages of colonization. Competitive exclusion is based on the introduction of nonpathogenic microbial mixtures into the gastrointestinal tract of neonatal animals, with the goal of either preventing pathogens from colonizing the intestine or by displacing pathogens that may have begun to colonize.[136]

Prebiotics

Prebiotics are sugars and other organic compounds that are indigestible to humans and animals but that can be broken down by certain types of beneficial gut microbiota. Prebiotics alter the composition of the gut microflora and help to exclude pathogenic bacteria because they provide essential compounds. All bacteria need nutrients. How many limited nutrients are available determines how much growth there can be. Whoever gets the most energy will flourish. Beneficial bacteria in the gut (for example, *Bifidobacteria* and *Lactobacilli*) help outcompete pathogens, even though the exact molecular mechanisms of action have so far largely remained unclear.[137]

Some experts think that the presence of beneficial microbiota often leads to other positive changes, for instance improvement for the host's immune system or metabolism, and that it can have other beneficial effects such as improved absorption of minerals.[138] In some cases, prebiotics favor specific members of the gut microflora that produce antimicrobial substances.[139] That can directly counteract pathogens.

Implementation Considerations for Pre- and Probiotics

In the U.S., most pre- and probiotics are not regulated as prescription drugs but rather as foods, dietary supplements, or medical foods.[140] This limits the claims under which these products can be marketed and the types of data that may need to be collected during potential regulatory approval.[141] Safety, purity, and potency may not have to be shown, and not all products require approval.[142]

While pre- and probiotics are believed to be very safe, some potential concerns exist. For probiotics, these include the risk of infection by probiotic strains, such as endocarditis in humans in response to certain *Lactobacilli*, and the potential for deleterious metabolic activities or immune deviations resulting from the shift in microbiota.[143] Microbiota may also transfer antimicrobial resistance or virulence genes to pathogenic bacteria in the gut.[144] Because probiotics consist of living microorganisms that can be susceptible to environmental factors such as heat, their manufacturing, storage, and administration can be more challenging than for prebiotics.

Prebiotics do not share most of the safety concerns associated with probiotics. However, prebiotics can only favor microorganisms that are present, so their efficacy depends on the beneficial bacteria already being in the gastrointestinal tract.[145] Because the microbiota is extremely complex, not completely characterized, and variable from individual to individual, prebiotics may generate different effects in different individuals.[146]

Anti-pathogenic strategies

Anti-pathogenic strategies may rely on the administration of substances toxic to the pathogen, such as bacteriocins and colicins, antimicrobial drugs, or sodium chlorate.[147] Other approaches include bacteriophages, which infect and kill certain pathogenic bacteria; and vaccines, which elicit immune responses that will inactivate the pathogen.[148]

Bacteriocins and colicins

Bacteriocins and colicins (a subset of bacteriocins produced by certain *E. coli* strains and toxic to other strains), are a diverse group of antimicrobial proteins that are produced by certain bacteria and are toxic to foodborne bacterial pathogens.[149] The spectrum of pathogens against which bacteriocins are active varies from narrow to broad and depends on the individual bacteriocin.[150] They employ a variety of mechanisms of action depending on the compound and the microorganism involved, including pore formation in the bacterial cell wall and the disruption of gene expression and protein metabolism.[151]

Implementation Considerations for Bacteriocins and Colicins

Bacteriocins are potentially attractive alternatives to antimicrobial drugs because their efficacy is independent of potential antimicrobial resistance traits and because they usually have low toxicity for the treated host.[152] Many bacteriocins can be produced at the site of infection by probiotic bacteria.[153] However, pathogens can develop resistance, even though the ease of resistance development likely depends on the mode of action for the specific bacteriocin and how easily the bacterium can alter its molecular targets.[154]

Antimicrobial drugs

Broad-spectrum antimicrobials such as neomycin sulfate can treat infection in livestock species and, in certain situations, reduce pathogen loads in the gastrointestinal tract before slaughter.[155] Even though these treatments can be very effective under certain circumstances, regulatory as well as nonregulatory concerns have to be considered in deciding on their use. Of particular concern is the role that these drugs play in the development of antimicrobial resistance.[156] Antimicrobial drugs can also interfere with live vaccines and disrupt the gut's microflora, potentially leading to increased susceptibility to subsequent infections with pathogens such as *Salmonella*.[157]

In the United States, veterinary drugs can be administered legally to food-producing animals only in accordance with specific label instructions determined during regulatory approval of the drug or, except for drugs administered through feed, in certain other clearly defined situations in which an unmet veterinary need dictates use outside of the conditions for which the drug is approved.[158] The label instructions typically specify the conditions the drug can treat and in which animals; the dose, frequency, and duration of administration; the route of administration; and the withdrawal time after dosage during which meat, milk, or eggs are not fit for human consumption. The potential use of antimicrobial drugs on farms and feedlots is therefore subject to regulatory restrictions.

Sodium chlorate

Sodium chlorate is toxic only to certain bacteria, such as *Salmonella* or *E. coli* that use an enzyme called nitrate reductase for their respiration.[159] This enzyme, which normally converts nitrate to nitrite, mistakes the structurally similar chlorate for nitrate and converts it to the highly toxic chlorite.[160] As chlorite accumulates in the cell, the pathogen is killed.[161] Sodium chlorate is not currently approved in the U.S.

Essential oils

Scientific data were insufficient to evaluate the efficacy of essential oils as potential pre-harvest interventions for the livestock species of concern in this report. Essential oils are very complex mixtures of volatile molecules generated by the secondary metabolism of aromatic and medicinal plants, which produces products that are beneficial for plant growth and may have antibacterial properties but is not directly involved in normal growth, development, or reproduction of the plant.[162] Essential oils differ in molecular structure and antimicrobial mode of action, which is often not completely understood on a molecular level but can range from bacterial cell wall and membrane disturbance to disruption of the bacterium's metabolism and protein synthesis or the damage of bacterial DNA.[163] Despite their potential promise, the use of essential oils has so far been limited by data gaps as well as the high concentrations that are typically required to achieve antimicrobial effects and the corresponding negative implications for the smell and taste of the meat or poultry.[164]

Heavy metals

Whether heavy metals may, under certain circumstances, be promising pre-harvest interventions is largely unclear. Data were insufficient to evaluate their efficacy for the livestock species of concern in this report. Certain heavy metals such as zinc and copper, which are essential in trace amounts, are commonly added in higher concentrations to the feed of pigs and poultry as growth promoters.[165] Growth promotion is believed to be caused by antimicrobial actions, similar to those caused by antimicrobial drugs; questions remain, however, about the exact mechanism of action.[166] High concentrations of heavy metals can lead to tissue residues that may cause human health concerns.[167] The use of heavy metals has also been associated with increased antimicrobial resistance, even though questions about the underlying drivers continue to be debated.[168]

Bacteriophages

Bacteriophages, which were discovered in 1915, are viruses that infect and kill bacteria.[169] Temperate bacteriophages can replicate through one of two mechanisms: lysogenic and lytic cycles.[170] In the lysogenic cycle, bacteriophage DNA is incorporated into the genome of the host bacterium, where it will lie dormant.[171] As the bacterial cell multiplies, the phage genome is also multiplied, just as any other part of the bacterial genome.[172] External factors will trigger the switch from lysogenic to lytic cycle. At that point, the bacteriophage DNA will be excised from the bacterial genome. Now the bacteriophage will actively replicate in the bacterial cell.[173] At some point, the bacterial cell will lyse (dissolve), liberating large quantities of new bacteriophages that can go on and infect new bacterial cells.[174] Obligate lytic bacteriophages replicate exclusively via the lytic cycle.[175]

Implementation Considerations for Bacteriophages

Most bacteriophages have a narrow host range, which in extreme cases can be restricted to a single strain of a bacterium.[176] Bacteriophages can therefore be used in a very targeted way with minimal unintended impacts on other bacteria.[177] In addition, bacteriophages have a low inherent toxicity for humans or animals, are not inhibited by antimicrobial resistance traits of the target pathogen, and are capable of replicating after administration, specifically where pathogens are located, which can simplify dosing.[178] Bacteriophages are common natural members of the microbiota on farms and feedlots, and have been used in several livestock species with promising results.[179] Bacteriophages have been developed for pre-harvest uses that target *Salmonella*, *Campylobacter*, *E. coli*, and *Clostridium perfringens*.[180] Bacteriophages targeting *E. coli* O157:H7 are currently available as cattle-hide washes and surface cleaning products.

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The narrow host range of most bacteriophages limits the development of resistance mechanisms by the pathogenic bacteria, but concerns about bacteriophage resistance development remain.[181] In addition, the narrow host range can limit the usefulness for practical applications.[182] Temperate bacteriophages have the potential for transmitting antimicrobial resistance or virulence genes.[183] At the transition from lysogenic to lytic cycle, the bacteriophage DNA is not always excised precisely from the host bacterium. Bacterial genes, including those that confer resistance to antimicrobial drugs or that lead to increased virulence, can be accidentally incorporated into the phage genome and may be transmitted to other bacteria during subsequent infections.[184] Other potential concerns for bacteriophage applications include stability under typical storage and use conditions and, in many cases, the absence of appropriate safety and efficacy studies.[185]

Vaccines

Vaccination is aimed at the development of immunity comparable to that which develops after natural infection, but without the negative impacts caused by the disease.[186] Vaccines have been widely used in veterinary medicine to prevent infections with viruses and bacteria that cause animal diseases and are promising approaches for pre-harvest food safety.[187] However, because most foodborne pathogens do not cause significant animal or production losses, economic incentives differ between food safety and animal health oriented uses.[188] A number of vaccines are currently available for pre-harvest food safety.[189] Yet, in several situations, traditional vaccines may not be cost-effective approaches for pre-harvest food safety at this time.[190] New vaccine technologies and new administration routes (such as feed-based instead of via injection, which reduces labor and other costs) may make certain vaccine uses for food safety more feasible in the future.[191]

A Summary of Vaccine Types

To achieve immunity, a decoy is presented to the immune system that is sufficiently similar to the target pathogen to elicit a protective immune response yet is nonpathogenic.[192] Conventional vaccines use either a live but nonpathogenic strain of the target pathogen (attenuated live vaccines) or the inactivated pathogen (killed vaccines). More recently, advances in biomedical research and bioengineering have led to the development of additional vaccine types (like subunit vaccines, vector vaccines, and DNA vaccines) designed to overcome challenges and limitations of conventional vaccination approaches.[193] The type of vaccine is important to consider because it can affect the robustness and longevity of immunity, the ability to protect against related but different strains, the ways by which a vaccine can be administered (through feed or water vs. injection), and the potential side effects.

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Attenuated live vaccines

Attenuated live vaccines typically induce a mild but subclinical infection of the vaccine strain.[194] Because the vaccine strain infects and multiplies in target cells, both cellular and humoral immunity develop in response to vaccination.[195] The adaptive immune system has two components: cellular and humoral immunity. Cellular immunity is based on the interaction of certain immune cells (T lymphocytes) with fragments of the pathogen that will be presented on the surface of infected cells. Humoral immunity is mediated by antibodies (that is, specific proteins secreted by other types of immune cells, B lymphocytes) that bind to and inactivate pathogens present outside of cells.[196] Natural infections usually generate both cellular and humoral immunity, and this combined immunity is generally superior to immunity based solely on one component of the immune system.[197] For this reason, live attenuated vaccines typically provide longer-lasting protection and broader cross-protection against heterologous strains (related but not identical to the vaccine strains—for instance, different *Salmonella* serotypes) of the pathogen than killed vaccines.[198] The vaccine itself is usually sufficiently immunogenic to elicit the immune response, so that adjuvants[199] are not needed, eliminating concerns about potential adjuvant residues or side effects.[200] In addition, because the vaccine strain will cause an infection, live vaccines can typically be administered in more convenient ways than injection, such as orally through drinking water, intranasally, or intraocularly.[201]

However, there is some risk of reversion, where the inactivated strain regains some or all of its pathogenicity.[202] For many commercial vaccines, the exact molecular changes that led to the attenuation of the pathogen have been defined, providing some scientific rationale to assess the risk of reversion.[203] Yet, some commercial bacterial vaccines have not yet been characterized to this extent.[204] In addition, because the vaccines contain live organisms, they are of limited stability and may require special treatment during manufacturing, storage, and administration.[205]

Killed vaccines

Because they do not contain viable pathogens, inactivated vaccines are typically more stable than live vaccines and pose no risk of reversion.[206] However, killed vaccines elicit only humoral immune responses, making them considerably less protective than live vaccines and more adept at controlling clinical symptoms of infection than at preventing the shedding of pathogens.[207] Because they are less immunogenic, killed vaccines typically require the addition of potent adjuvants to elicit adequate immune responses, which raises concerns about potential adjuvant residues as well as side effects that may, for instance, lead to decreased daily weight gains in animals.[208] The need for adjuvants also results in higher production costs compared to live vaccines. Killed vaccines must be administered by injection, rendering labor costs prohibitively expensive in certain production systems.[209]

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Novel vaccines

A variety of new biomedical approaches have been applied to vaccine development. DIVA (differentiating infected from vaccinated animals) vaccines are currently available for livestock. Other groundbreaking technologies may allow researchers to overcome some current vaccine challenges.

DIVA or marker vaccines are derived from pathogens that have been genetically engineered to not generate certain proteins they would normally produce or to generate additional proteins they normally would not.[210] Because no antibodies are generated against absent proteins or additional antibodies are directed against the added proteins, specific diagnostic tests based on the absence or presence of antibodies against specific proteins allow vaccinated animals to be distinguished from naturally infected animals. This allows the use of vaccination without interfering with serological surveillance (in other words, surveillance for pathogens based on the testing for antibodies).[211]

Other new approaches include subunit vaccines, which are vaccines that contain only those parts of the pathogen against which protective antibodies are directed. In traditional vaccines a large fraction of antibodies are directed against parts of the pathogen that are not directly involved in infection, resulting in a large number of antibodies that will not protect effectively against infection.[212]

Vectored vaccines are nonpathogenic organisms—vectors—often not related to the target pathogen, which are genetically engineered to express certain parts of the pathogen.[213] They are meant to elicit an immune response that protects against the pathogen. Because the vector will infect and multiply in cells, these vaccines can elicit humoral and cellular immunity and generally do not pose a risk of reversion to the target pathogen, but immune responses against the vector can cause potentially significant side effects.[214]

DNA vaccines are based on the physical introduction of pathogen DNA into the host cell, which in response will express parts of the pathogen.[215] Because only certain parts of the pathogen are expressed, there is no risk of reversion; and because no vector is used, there is no risk of immune responses against the vector.[216] At the same time, the vaccine generates cellular immune responses and is more stable than live or vectored vaccines.[217] Administration of the vaccine has remained somewhat challenging, and veterinary DNA vaccines have to date remained largely experimental, even though two DNA vaccines have been licensed in the U.S., one for horses against West Nile virus and one for fish.[218]

Exposure-reduction strategies

These strategies aim to prevent the animals from being exposed to the pathogens in the first place.

Biosecurity

Replacement animals, farm staff and visitors, equipment, vermin, wildlife, pets—all of these can introduce pathogens to farms.[219] Farm biosecurity practices are designed to minimize the risk of pathogens from such sources by restricting or preventing access, enforcing quarantine practices, and rigorously cleaning and sanitizing equipment.

Water quality and hygiene

Water, particularly from nonmunicipal sources, is widely recognized as a potential source of pathogens such as *Salmonella* or *E. coli* O157:H7 on farms and feedlots.[220] In addition, water troughs and other water-distributing devices can serve as a reservoir for pathogens.[221] Potential intervention methods include the regular cleaning of water systems, the use of municipal water sources, and the treatment of well water with chlorine, organic acids, or other substances to inactivate pathogens.[222] Some water additives can affect the taste and palatability of the drinking water, with potential negative economic and animal health impacts. In some production systems, water can be used to distribute vaccines, animal drugs, or other substances. Water characteristics such as pH, hardness, and temperature can have a negative impact on some of these substances and have to be tightly controlled to ensure accurate dosing.

Feed hygiene

Adequate feed that meets an animal's nutrient requirements is a prerequisite for overall animal health. Similar to water, feed can introduce pathogens such as *Salmonella* or *E. coli* O157:H7 on farms and feedlots.[223] Contamination can occur at many points along the feed chain, from primary production through processing, transportation, and storage on farms or feedlots. Feed hygiene includes the selection of reliable sources that minimize the risk of obtaining contaminated feed, as well as the appropriate storage and handling on the premises to prevent access of vermin, wildlife, and pets, and to control humidity.[224] Certain feed characteristics can, in some cases, affect the microbial composition in the gastrointestinal tract.[225]

Housing

Housing choices—for example, flooring type, ventilation, temperature, animal density—affect animal health and well-being. Improper housing can lead to greater stress and injuries.[226] Crowded housing also increases contact between animals and their manure, which can affect the spread of foodborne pathogens on a farm or feedlot.

Appendix D: Efficacy of pre-harvest interventions for poultry

Note: These findings are a result of a review of the published literature as well as an expert panel convened by Pew to discuss specific intervention strategies in poultry. Tables summarizing comments by the expert panel on specific interventions are included.

Prebiotics

Several studies have shown positive effects of prebiotics such as fructooligosaccharide on *Salmonella* colonization and shedding rates in broiler chicken. For instance, administration of this prebiotic to 1-day-old chicks, followed by exposure to *Salmonella* 21 days later, led to statistically significant reductions in *Salmonella* carriage in the gut, even though equivalent efficacy was not seen in the comparable experiment performed with *Salmonella* seven days after fructooligosaccharide dosing.[227] Another study comparing several prebiotic formulations found variable results, which included both increases and decreases in *Salmonella* colonization depending on the oligosaccharide and formulation used.[228]

Experimental studies suggest that prebiotics may be helpful to offset increases in *Salmonella* colonization caused by stress.[229] However, more studies, including large field trials in commercial flocks, are needed to evaluate efficacy under real-world conditions and to determine the optimal way to incorporate prebiotics into pre-harvest food safety systems on poultry farms. A meta-analysis of feed additives found that prebiotics had a statistically significant effect on the prevalence of *Salmonella* in the gut of broiler chicken, but the primary research studies were of weak quality and had major deficiencies in experimental design and reporting, raising concerns about the validity of the findings.[230]

Table D-1

Benefits, Limitations, and Data Gaps of Prebiotics in Poultry

Benefits	Limitations	Data gaps
Yeast-cell products are promising for *Salmonella* Thought to stimulate immune system Have been shown to help control different pathogens Numerous products on the market Used in breeders during raising phase and in broilers Easy to administer with feed Relatively cheap Reasonably large amount of scientific evidence available	Cannot control all microbial issues in flock Not promising for *Campylobacter*	Mechanisms of action Not a lot of work in recent years

Probiotics

Probiotics have been proposed as potential alternatives to antimicrobial growth promoters in broilers[231] and are generally regarded as promising approaches for reducing *Salmonella* shedding, even though experimental studies can be difficult to evaluate due to the potential impact of external factors such as stress or feed withdrawal.[232] An expert group convened by the Food and Agriculture Organization of the United Nations and the World Health Organization found competitive exclusion products effective at reducing *Salmonella* but not *Campylobacter*, emphasizing differences between the two pathogens.[233] Combining probiotics and prebiotics may have a synergistic effect in poultry; this strategy has been evaluated in experimental studies, although some studies failed to find a significant effect of the products used alone or in combination.[234]

Competitive exclusion to control *Salmonella* infection in broiler chicks from the time of placement has been studied extensively; this strategy seems highly promising.[235] A systematic review and meta-analysis of studies analyzing 14 different competitive exclusion products in broiler chicken, most of them conducted under laboratory conditions, concluded that competitive exclusion products—undefined as well as partially defined and commercial products—had the potential to reduce the prevalence of *Salmonella* colonization over time.[236] Undefined products tended to outperform commercial products with a few exceptions. More studies in commercial flocks under realistic conditions are needed.

Table D-2

Benefits, Limitations, and Data Gaps of Probiotics in Poultry

Benefits	Limitations	Data gaps
Competitive exclusion products		
Potentially effective against *Salmonella* Easy to implement, especially in feed; water a bit more complicated	Not currently used in poultry Limited products with FDA approval Too expensive to be feasible Efficacious only if given very early Complex to produce and ship Not effective against *Campylobacter* Affects bacterial load shed more than prevalence Can interfere with live vaccines Can increase biofilm in waterline, especially if sugar carrier; may not have practical impacts on intervention choices, though Moderate to high cost	More research has been focused on application in broilers than broiler-breeders Impact of various external variables on efficacy Quantitative reduction in *Salmonella* shedding for a given situation (e.g., bird age, season, *Salmonella* strain) Effectiveness across serotypes and subtypes (e.g., individual *S.* Typhimurium strains)

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Undefined direct-fed probiotic		
Effective against *Salmonella* Most effective probiotics Combination of multiple bacterial species most effective Easy to implement, especially in feed; water a bit more complicated Considerable research available on efficacy	No FDA approval route because lacking definition of strains; none currently approved as drug Not effective against *Campylobacter* Cannot be given in ovo (embryo will not hatch) Affects bacterial load shed more than prevalence Can increase biofilm in waterline (especially if sugar carrier); may not have practical impacts on intervention choices Potential risk for antimicrobial resistance transfer Moderate cost	Composition of bacterial strains Potential variability in mode of action across products and bacterial strains Differences among strains of bacterial species Differences in efficacy across farm locations and with time Interactions with the microflora in the poultry's gut Impact of changes in feed (e.g., starter feed to grower feed) Quantitative reduction in *Salmonella* shedding for a given situation (e.g., bird age, season, *Salmonella* strain) Effectiveness across serotypes and subtypes (e.g., individual *S.* Typhimurium strains)
Defined direct-fed probiotic		
Effective against *Salmonella* Heat-stable probiotics (e.g., spore formers, *B. subtilis*, *B. licheniformis*) can be given with pelleted feed; easier to administer; seem to have better efficacy Less effective than undefined probiotics Products on market Administration through feed most promising Easy to implement, especially in feed; water a bit more complicated Considerable research available on efficacy	Non-heat-stable probiotics have to be added through water Water additives can be difficult to give (e.g., dosing, water quality and waterline system, not compatible with water disinfectants, etc.) Administration as mist in hatchery complicated (e.g., interactions with vaccinations) Not effective against *Campylobacter* Can be given in ovo but administration to reach the gut variable and possibly difficult to control Affects bacterial load shed more than prevalence (reduce *Salmonella* spreading through the flock) Can increase biofilm in waterline (especially if sugar carrier); may not have practical impacts on intervention choices Moderate cost	Variability in mode of action Differences among strains Genetic determinants of specific strain characteristics Differences in efficacy across locations and time Interactions with the microflora in the poultry's gut Impact of changes in feed (e.g., starter feed to grower feed) Quantitative reduction in *Salmonella* shedding for a given situation (e.g., bird age, season, *Salmonella* strain) Effectiveness across serotypes and subtypes (e.g., individual *S.* Typhimurium strains)

Bacteriocins and colicins

Bacteriocins have shown tentatively promising results against *Campylobacter* infection in broilers and turkeys, at least under experimental conditions.[237] Promising results have also been reported for *Salmonella*.[238] However, more studies in commercial flocks under realistic conditions are necessary to evaluate efficacy against both pathogens.

Table D-3

Benefits, Limitations, and Data Gaps of Bacteriocins and Colicins in Poultry

Benefits	Limitations	Data gaps
Efficacious in laboratory studies	Not used in real-world conditions No commercial product on market Limited scientific data available Cost of implementation currently not clear	Experimental studies under commercial conditions

Antimicrobial drugs

Similar to the situation for pigs, international experts agree that *Salmonella* control in poultry flocks should generally not rely on antimicrobials.[239] Antimicrobial use carries the risk of resistance emergence. However, potentially even more important for poultry is the risk of disrupting the natural gut microflora and thereby increasing susceptibility to *Salmonella* infection. In fact, cases of *Salmonella* spreading throughout a poultry flock after antimicrobial treatment have been documented in the literature.[240]

Even though in some cases antimicrobial treatments have been shown to decrease the risk of *Campylobacter* colonization of broiler flocks (to treat respiratory infections, for instance), results overall have been variable and the use of antimicrobials to control *Campylobacter* infection in broilers is strongly discouraged by experts.[241]

Sodium chlorate

Experimental studies of *Salmonella* have shown promising results for sodium chlorate in poultry.[242] For instance, adding sodium chlorate to drinking water shortly before slaughter has been shown to reduce crop (that is, the part of the avian digestive tract that precedes the stomach and is used to store food prior to digestion) colonization during subsequent feed withdrawal, at least under experimental conditions.[243] Similarly, a meta-analysis of feed additives showed a statistically significant protective effect of sodium chlorate on *Salmonella* concentrations in the gut of chickens, even though the quality of study design and reporting in the primary research studies was low.[244] More, better-designed studies, particularly large field trials under realistic conditions, are needed to substantiate the efficacy of sodium chlorate as a pre-harvest intervention for *Salmonella* in poultry.

Table D-4

Benefits, Limitations, and Data Gaps of Sodium Chlorate in Poultry

Benefits	Limitations	Data gaps
Effective against facultative anaerobic bacteria (e.g., *Salmonella, E. coli, Clostridium*) Can act synergistically with probiotic Likely administration in hatchery and right before harvest, or throughout the rearing process Residue profile not different than if given sodium chloride solution Easy to implement, especially in feed; water a bit more complicated Compound is cheap	Not commercially available Causes wet litter if concentration is too high (increases water uptake with diet) Affected by water (e.g., NaCl concentration in water), not as easily taken up through feed as water Limited data available on efficacy under field conditions Very scarce data in breeders No effect on *Campylobacter*	Field studies under real-world conditions

Bacteriophages

Scientific studies have shown somewhat modest yet clearly beneficial effects in poultry, at least under experimental conditions.[245] Some evidence suggests that reductions in pathogen loads may be relatively short-lived, emphasizing the value of phage cocktails containing multiple strains. Notably, treating *Campylobacter* infection a few days before slaughter may be the most effective and feasible use for bacteriophages.[246]

The potential value of phages for pre-harvest interventions against *Campylobacter* in poultry is indicated by modeling studies. Mathematical models have been developed to estimate the costs and benefits of developing bacteriophages to reduce *Campylobacter* in broilers prior to slaughter. This intervention ranked third in efficiency out of nine scenarios evaluated in a New Zealand model that looked at pre- and post-harvest measures. Bacteriophages were also found to be highly cost effective for reducing the burden of illness of *Campylobacter* in poultry. To develop and treat broilers with these phages, the study estimated, would cost close to $3 million.[247]

A Dutch model evaluated the impact of bacteriophages in reducing the number of *Campylobacter* infections in humans and estimated that when phages reduce the concentration of *Campylobacter* in broiler feces by a factor of 100, the risk to consumers would be reduced by 75 percent. When the concentration of *Campylobacter* was decreased by a factor of 10, the risk reduction was still present but smaller, 45 percent. On average, the study estimated that this intervention would cost the broiler industry 7 million euros a year. A scenario in which only *Campylobacter*-positive flocks were treated was estimated to cost the industry approximately 4 million euros a year.[248] However, under this scenario, the decrease in risk to the consumer was smaller, varying from 50 to 70 percent, depending on the test method chosen. The less-significant reduction in human illnesses was because of test fallibility in which positive flocks are missed.

More studies, including large field trials on commercial operations under real-world conditions, would be needed to truly evaluate the efficacy of bacteriophages as pre-harvest interventions.

Table D-5

Benefits, Limitations, and Data Gaps of Bacteriophages in Poultry

Benefits	Limitations	Data gaps
Efficacious in laboratory setting Used in water under experimental conditions Can be used for other pathogens than *Salmonella* *(Campylobacter)* Commerical product (spray treatment) used for processing plants	Not used on farms Do not work consistently Very serotype-specific or even specific to individual strains within a serotype (i.e., isogenic phages) Will not survive pelleting process for feed Difficult to administer Commercial cost currently unclear Limited data available in the English literature	Experimental studies under commercial conditions

Vaccines

Both live and killed *Salmonella* vaccines are available commercially.[249] A recent EFSA opinion on the use of vaccination in poultry concluded that it can be a helpful component of a *Salmonella* control program in broiler, breeder, and grandparent flocks, which can be used throughout the life of the bird (if vaccination can be reliably differentiated from natural infection, for instance through DIVA vaccines). Based on the limitation of available vaccines to date, vaccination may be more challenging for control programs targeting serotypes other than Typhimurium and *enteritidis*. In addition, vaccination may not be effective in eradication programs because vaccinated birds may still shed some *Salmonella*.[250]

Several studies, including in commercial settings, have repeatedly demonstrated the efficacy of vaccinating broiler-breeders to reduce *Salmonella* prevalence and load in broiler chicken.[251] One of the studies showed a significant reduction in the prevalence of *Salmonella* in broilers entering the processing plant for poultry companies that used the vaccination program for its breeders. The environment of broiler farms that received chicks from vaccinated breeders also had lower prevalence of *Salmonella*.[252] Another study from the same group did not detect the same decrease in environmental contamination; however, it confirmed that broilers from vaccinated breeders had lower prevalence than the ones from unvaccinated birds. This study also found that the load of *Salmonella* was 50 percent lower for broiler chickens from vaccinated breeders.[253] Vaccination of egg-laying hens is also considered to be a main reason for the significant decline in human *S. enteritidis* infections in countries such as the United Kingdom.[254]

Currently, no vaccines are commercially available to control *Campylobacter* in poultry. There are, however, some promising targets that could be used to develop such products in the future.[255] In fact, some experimental studies have been highly successful, particularly for live vaccines, even though reproducibility has been challenging and vaccine field trials are needed to ultimately evaluate efficacy.[256]

Table D-6

Benefits, Limitations, and Data Gaps of Vaccines in Poultry

Benefits	Limitations	Data gaps
Live vaccines		
Effective for controlling *Salmonella* Vaccination of broiler-breeders shown to affect *Salmonella* load in processing plant Consistently effective Some cross-protection against multiple serotypes Used in broiler-breeders Vaccines on the market Reduces bacterial load on carcasses Generates maternal antibodies for *Salmonella* Relatively easy to administer (e.g., water, spray) Limited interference with serology Considerable research available on effectiveness	Limited cross-protection against other *Salmonella* serotypes No long-term protection; may need to readminister or combine with inactivated vaccine Vaccines can be expensive; may be too expensive for routine use in broilers No vaccines available for *Campylobacter*	Field studies in actual facilities Case-control studies in real-world settings Vaccine trials for *Campylobacter*
Inactivated vaccines		
Effective for controlling *Salmonella* Vaccination of broiler-breeders shown to affect *Salmonella* load in processing plant Used in broiler-breeders Consistently effective Longer-term protection than live vaccines Reduce bacterial load on carcasses Commercial products for *S. enteritidis* and one for multiple strains with some cross-reactivity Most inactivated vaccines currently used are autogenous Generates maternal antibodies for *Salmonella* Easy to implement, though labor-intensive Considerable research available on efficacy	No or limited cross-protection against multiple serotypes Not economical in broilers Autogenous vaccines have no information on efficacy (due to regulatory limitations) No vaccines available for *Campylobacter* Endotoxins can cause depression and effects on feed consumption Humoral immune response can create serological cross-reactivity (e.g., false-positive results for *S.* Gallinarum-Pullorum, potential surveillance program issues in the U.S. and other serological surveillance systems) Vaccine and labor can be expensive Not used in broilers	Field studies in actual facilities Case-control studies in real-world settings Vaccine trials for *Campylobacter* Efficacy in broilers

Biosecurity

Biosecurity is generally believed to be the most effective intervention against *Campylobacter* in broiler and turkey farms. Scientific studies evaluating the efficacy of biosecurity measures are generally scarce, but several studies available for *Campylobacter* strongly suggest the effectiveness of biosecurity interventions for this pathogen.[257] Preventing the influx of flies into broiler houses, for instance, has been shown to significantly reduce the prevalence of *Campylobacter*-positive flocks in Denmark.[258] Other biosecurity measures such as standardized cleaning and disinfection of the poultry house before placement and standard hygiene protocols for farm personnel have been shown to reduce *Campylobacter* prevalence in broiler flocks, measured 42 days after placement, by more than 50 percent.[259] Reductions in slaughter age, discontinuing of thinning, and exclusion of insects such as flies and beetles from the chicken house[260] have also been shown to be effective mitigation options.[261]

Biosecurity is also believed to be important for *Salmonella* control, but quantitative studies to assess efficacy are scarce. Because of the larger number of potential sources for *Salmonella* introduction into poultry farms, the role of biosecurity as a pre-harvest intervention for *Salmonella* may be more complex than for *Campylobacter*.

Table D-7

Benefits and Limitations of Biosecurity in Poultry

Benefits	Limitations
One of the only things that can be effective for *Campylobacter* Very important for *Salmonella* as well	Can be difficult to implement Implementation expensive

Feed and water

Because contaminated feed can be an important source of *Salmonella* and other pathogens, controlling it in poultry feed has received considerable attention.[262] Pelleted feed may be somewhat safer than nonpelleted feed due to the additional heat processing steps. In fact, one experimental study showed that the risk of *Salmonella* in chicken decreased when feed was heated above 83 degrees Celsius (181 degrees Fahrenheit) and processed into pellets.[263] Acidified feeds have been proposed as a strategy to reduce *Campylobacter* and *Salmonella* in broiler chickens, but experimental results have remained variable.[264]

As with cattle and swine, certain types of feed and feeding practices have been associated with changes in the concentration of pathogens, presumably at least in part because of physiological mechanisms that alter the gut microflora, by promoting or hindering the colonization of pathogens, or by changing the amount of time feed is exposed to gastric acids that can inactivate pathogens. For instance, studies have shown that plant protein-based feed can reduce the colonization of *C. jejuni* in chicken.[265]

Several feed additives have been studied. An extensive literature review found that organic acid additives (like lactic acid and acetic acid) reduced the number of *Campylobacter*-positive flocks;[266] however, the high cost of some of these additives could be a barrier to adoption, and field trials are needed to confirm the impact under real-life situations.[267] In addition, results appear to vary with the type of organic acid used.[268] According to other studies, chicken had a lower incidence of both *Campylobacter* and *Salmonella* when they drank water treated with organic acid additives.[269] A recent field study showed that *Campylobacter* levels in broilers decreased when given acidified water; nevertheless, decreased pathogen levels in the drinking water had no effect on the concentration of pathogens in the broiler carcasses at processing.[270] More field trials under realistic conditions are needed to evaluate the impact of feed and water treatments.

Table D-8

Benefits, Limitations, and Data Gaps of Feed and Water Additives in Poultry

Benefits	Limitations	Data gaps
Organic acids in water		
Effective in high-load situations Replaces acid generated by *Lactobacillus* during feed withdrawal prior to harvest Used during first and last week of life Works primarily in crop; limited impact in caecum (because of buffering capacity of intestine) but some potential impact on caecal load Reduce colonization of crop, which is primarily caused by coprophagia (i.e., the intentional ingestion of feces) Easy to administer (but need to get concentration right; high pH can affect efficacy) Reasonable body of scientific evidence available on efficacy	Not routinely used by most farmers Not used as much in breeders as in broilers (may be used in feed for breeders in the future) Palatability issues if used in higher concentration; potential weight losses going into the slaughterhouse Potential damage to equipment (e.g., medicators) Cheap if administered through water; feed-based organic acids not yet well understood and cost not clear	Experimental studies under commercial conditions
Water disinfection (e.g., chlorination)		
Continuous application to chlorinate water from nonmunicipal sources Works very well against *Campylobacter* Relatively easy to administer but some limitations (e.g., dose, mixing, pH) Relatively cheap Considerable amount of scientific data available	Substitute for municipal water source Potential for equipment damage (depends on factors such as water hardness)	
Essential oils (e.g., oregano)		
Some antibacterial efficacy Promising against *Clostridium* and *Salmonella* Products on the market	Limited scientific data available Potentially less effective in the field than in experimental studies Not very well understood Cost of implementation currently not clear Data on efficacy among breeders very scarce	Experimental and field studies under commercial conditions Experimental studies in breeders Ease of application depends on heat stability and formulation; real-world use fairly unclear

Appendix E: Efficacy of pre-harvest interventions for cattle

Note: These findings are a result of a review of the literature as well as an expert panel convened by Pew to discuss specific intervention strategies in cattle. Tables summarizing comments by the expert panel on specific interventions are included below.[271]

Prebiotics

In cattle, the use of prebiotics has been largely limited by the structure of their digestive system. As with other ruminants, this tract is characterized by the rumen, a large digestive chamber that forms the first chamber of the alimentary tract and serves as a site for extensive microbial fermentation. With the exception of milk-fed calves (which consume milk rather than plant materials), cattle rely on microorganisms in the rumen to break down the indigestible plant materials (primarily cellulose) they ingest into digestible substrates. The rumen microbiota tends to digest and destroy most prebiotics, rendering them ineffective. New technologies such as coatings or genetically engineered plants are being developed to allow for the generation of commercial prebiotics that may be protected from the rumen microbiota.[272] Coupling the use of probiotics and prebiotics may have a synergistic effect and could be a potential control strategy in cattle.[273]

Table E-1

Benefits, Limitations, and Data Gaps of Prebiotics in Cattle

Benefits	Limitations	Data gaps
Easy to administer Likely wide consumer acceptance	Limited/no usefulness in ruminating animals due to degradation in the rumen Potentially high economic cost Potential for niche alteration	Substances to prevent breakdown during rumen passage Impact on environmental shedding Ability to verify adoption

Probiotics

A probiotic formulation containing *Lactobacillus* and *Proprionibacterium* is commercially available in the U.S. and widely used on large feedlots to improve growth efficiency and reduce pathogens, demonstrating economic feasibility, at least in certain situations.[274]

In experimental studies in cattle, the efficacy of different probiotics has primarily been evaluated for animal performance, such as average daily gains, and reductions in fecal shedding of *E. coli* O157:H7. While results for animal performance impacts were consistently positive, variable results have been obtained for *E. coli* O157:H7, ranging from no observed effect to a statistically significant reduction in fecal shedding.[275] These differences in efficacy were likely in part due to differences in experimental design (such as research farm vs. commercial feedlot, experimental vs. natural infection) and/or differences in the probiotic strains or mixtures used.[276]

Results from various studies, including systematic reviews and meta-analyses, suggest that probiotics, added to feed as direct-fed microbials, can significantly reduce the shedding of *E. coli* O157:H7 in beef cattle after natural infections, under the right circumstances.[277] In a meta-analysis, a combination of *L. acidophilus* (NP51) and *P. freudenreichii* (NP24), fed in high doses (10^9 colony-forming units per animal per day), was determined to be the most efficacious probiotic combination for reducing the prevalence of *E. coli* O175:H7 in feces, although differences among evaluated combinations were not statistically significant.[278] Similar conclusions were reached in reviews from USDA's Agricultural Research Service and Food Safety and Inspection Service, which also concluded that direct-fed microbials containing certain *L. acidophilus* strains, potentially in combination with *Propionibacterium*, are beneficial in reducing shedding of *E. coli* O157:H7 in feedlot cattle, even though not all *L. acidophilus* strains may be effective.[279] For example, a recent randomized control trial on a commercial feedlot failed to find a significant impact of a commercial *L. acidophilus*-based direct-fed microbial on fecal shedding, measured as within-pen prevalence.[280]

In experimental studies, probiotics reduced the prevalence of *E. coli* O157:H7 fecal shedding in feedlot cattle by up to 50 percent.[281] Few studies to date have evaluated the concentration of *E. coli* O157:H7 shed by infected animals. Most studies have been performed in cattle housed on research farms; efficacy on commercial feedlots may be lower.[282] Nonetheless, a mathematical model developed by the Public Health Agency of Canada generated quantitative estimates of the efficacy of probiotics as pre-harvest interventions in cattle. The model estimates that when probiotics are used, the average probability of human illness per serving of ground beef is reduced significantly compared with a baseline scenario without interventions.[283]

Table E-2

Benefits, Limitations, and Data Gaps of Direct-Fed Microbial Probiotics in Cattle

Benefits	Limitations	Data gaps
For some products, consistent reduction in prevalence and concentration of *E. coli* O157:H7 demonstrated at higher probiotic doses One commercial product currently widely used in feedlots Easy to implement on large feedlots (potential practical limitations in certain other settings, such as cow-calf operations or small feedlots) Relatively low economic cost Likely more widely accepted by consumers than some other interventions Impact on environmental shedding	Efficacy highly variable (by products, pathogens, strains) No FDA drug approval (i.e., no label claims or potency information) GRAS approval No specific GMPs, QA/QC, validation No specific assays (e.g., for determination of dose, strain composition, viability) Difficult to verify adoption Potential for niche alteration	Mechanism of action Evaluation of efficacy (currently only available for few probiotics) Efficacy in dairy cows and calves (data currently focused on feedlot cattle) Efficacy for pathogens other than *E. coli* O157:H7

Competitive exclusion probiotics, in some experimental studies, have been shown capable of displacing *E. coli* O157:H7 from the gastrointestinal tract of calves and effective at reducing shedding of Shiga toxin-producing *E. coli* strains.[284] However, the use of competitive exclusion in cattle has been limited because of the complex and changing gastrointestinal microflora, especially as the rumen develops and becomes functional and because of the long and complex production cycle from birth to slaughter.[285] To be approved for commercialization in the U.S., the microbial composition of competitive exclusion products, including the levels and types of organisms present, have to be fully characterized. This poses a challenge because these types of products tend to be highly complex mixtures of many strains that may vary in composition from lot to lot.

Table E-3

Benefits, Limitations, and Data Gaps of Competitive Exclusion Probiotics in Cattle

Benefits	Limitations	Data gaps
Short-lived animal health impacts in calves possible Easy to administer Likely wide consumer acceptance Likely impact on environmental shedding	Limited impact on food safety Time between administration and harvest too long in ruminants for treatment to remain effective Microbial changes during rumen development limit usefulness Potential for niche alteration	Mechanism of action Efficacy in calves Ability to verify adoption

Bacteriocins and colicins

Data on bacteriocins and colicins in cattle remain limited, and large-scale field trials in feedlot cattle are lacking. Bacteriocin-producing probiotics have been used successfully under experimental conditions to reduce fecal shedding of *E. coli* O157:H7 in calves.[286] New production methods may allow the cost-effective use of purified bacteriocins in the future, but experimental studies are missing.[287] It has been demonstrated in vitro that *E. coli* O157:H7 strains can develop resistance to colicins, primarily if challenged with a single type of colicin.[288]

Table E-4

Benefits, Limitations, and Data Gaps of Bacteriocins and Colicins in Cattle

Benefits	Limitations	Data gaps
Potentially more useful if administering probiotic strains that generate bacteriocins (limited data on efficacy available) Easy to administer	Efficacy in ruminating cows unclear Production in large quantities challenging Degradation in rumen (shielding possible but challenging) No delivery mechanism ready to market Potentially high economic cost Potentially less acceptable to consumers than some other interventions Potential for niche alteration	Data on efficacy in ruminating cows Ability to verify adoption Impact on environmental shedding

Antimicrobial drugs

The impact of several antimicrobial drugs, administered through feed, water, or injection, on shedding of *E. coli* O157:H7 in feedlot cattle and small ruminants has been evaluated in several experimental and field trials, with varying results.[289] A variety of drugs (for instance, ionophores, monensin, lasalocid, tetracycline) failed to show a statistically significant impact on fecal shedding, even though inadequate sample size and resulting low statistical power may have been an issue in some studies.[290] Neomycin sulfate, administered for two days via water, significantly reduced *E. coli* O157:H7 fecal shedding and concentrations on hide.[291] In the U.S., neomycin sulfate is not currently approved as a pre-harvest intervention for *E. coli* O157:H7, although it is approved for the treatment and control of colibacillosis. The risks and benefits of neomycin as a pre-harvest food safety intervention have to be weighed carefully.[292] In the U.S., extra-label uses of animal drugs have to meet the provisions outlined in the Animal Medicinal Drug Use Clarification Act and are prohibited for drugs added to animal feed.[293]

Table E-5

Benefits, Limitations, and Data Gaps of Antimicrobial Drugs in Cattle

Benefits	Limitations
Therapeutic use 2-3 days pre-harvest (with 1-day withdrawal) through medicated feed or water has proved efficacious in feedlot settings against *E. coli* O157:H7 Field-trial efficacy data available Easy to administer Easy to verify adoption	Potential problems associated with use of antimicrobials include selection for highly resistant strains, risk of drug residues, potential risk of environmental accumulation and exposure Inconsistent efficacy at lower doses and for other products, pathogens, and strains Potentially high economic cost Potentially limited consumer acceptance Limited impact on environmental shedding

Sodium chlorate

Experimental studies have evaluated the impact of sodium chlorate in feed or water on fecal shedding of *E. coli* O157:H7 in feedlot cattle and small ruminants.[294] Results consistently showed a reduction of *E. coli* O157:H7 shedding in response to sodium chlorate treatment, even though the effect was not statistically significant in all cases.[295] Sodium chlorate is not currently approved in the U.S. Approval will be required before any widespread commercial use may be considered.[296]

Table E-6

Benefits, Limitations, and Data Gaps of Sodium Chlorate in Cattle

Benefits	Limitations	Data gaps
Promising results in reducing fecal loads of a broad spectrum of pathogens in small-scale studies No negative impact on biological population of the rumen/intestine Low toxicity Easy to administer (if given as top-dress in animal feed)	No market approval Useful primarily at very specific points peri-harvest, and primarily for certain high-stress situations Not tested systematically; no field data available Potentially limited consumer acceptance Potential for chemical side effects (e.g., chemical exposure, corrosion) Limited to no impact on environmental shedding	Use under realistic field conditions (currently small-scale experimental studies only) Potential for development of resistance Correlation between reduction in fecal load and contamination of hides Efficacy if used in dairy cows Economic cost (mass-quantity chemical of low economic cost but some potential for price increase after FDA approval and potential patent protection) Ability to verify adoption (depending on potential assay development during FDA approval process)

Bacteriophages

Bacteriophages targeting *E. coli* O157:H7 are currently commercially available in the U.S. as cattle-hide washes and surface cleaning products, but not as feed additives.

Naturally occurring bacteriophages are commonly present on U.S. feedlots.[297] A number of studies have evaluated the impact of bacteriophage treatments on the shedding of *E. coli* O157:H7 in calves, steers, and sheep, with somewhat variable results.[298] Experimental studies of oral phage administrations in adult animals have primarily been performed in sheep, but results may be applicable to cattle given the physiological similarities.[299] In general, mixtures of multiple phages appear to be more effective than a single phage, and cocktails of up to 37 strains have been used in experimental studies.[300]

Phage cocktails, administered orally, generally lead to an initial decrease in the presence of *E. coli* O157:H7 in the intestine and feces, but in some studies results were short-lived and lasted less than two days.[301] Oral and topical administration to the area of presumably greatest contamination risk during slaughter (the recto-anal junction, where the last part of the gastrointestinal tract transitions into the anus), which prevents potential bacteriophage inactivation during gastrointestinal passage, also showed a decrease in *E. coli* O157:H7 contamination, even though some *E. coli* O157:H7 cells remained on the treated animals.[302] More studies are clearly needed to evaluate efficacy, particularly of oral administrations, on commercial feedlots, against other important cattle pathogens, and to determine the most appropriate administration (for instance, dose, frequency, administration route) for cattle.[303]

Table E-7

Benefits, Limitations, and Data Gaps of Bacteriophages in Cattle

Benefits	Limitations	Data gaps
Fairly widely used as hide-spray (seasonal use) Relatively low economic cost if administered to hide; potentially higher if administered in diet Easy to verify adoption if administered to hide; less clear for administration through diet	Data on efficacy (i.e., reductions in prevalence and concentration) very limited Potential evolution of the phage Potential for selection of resistant bacterial strains and transmission of microbial resistance or virulence genes among bacterial hosts (primarily of concern for use in diet) May require continuous dosing Efficacy may be specific to certain pathogens and strains Efficacy may differ between hide-spray and oral administration Potentially challenging to implement (e.g., labor intensive, implementation dependent upon seasonal and climatic factors) Potentially limited consumer acceptance Limited to no impact on environmental shedding	Methodology to clearly prove efficacy (current analytical limitation) Differences between use under laboratory conditions and on live animals complicate extrapolation of data More efficacy data Data on evaluating efficacy for dairy cows Cost of administration through diet

Vaccines

In addition to various inactivated and modified live vaccines licensed to prevent animal diseases caused by infections with *Salmonella*, *E. coli*, or related pathogens, two pre-harvest-focused, inactivated vaccines are currently commercially available in the U.S. under conditional licenses, one to reduce the prevalence of *E. coli* O157:H7 and the other to reduce disease from *Salmonella* Newport in cattle. In addition, autogenous vaccines are available under a conditional license. These are inactivated vaccines made specifically for a given herd or premises, and based on the specific pathogens present in that herd.

Autogenous vaccines can be made against a variety of pathogens and strains, and can be useful in protecting against strains for which no effective commercial vaccines are available, such as certain *Salmonella* strains that may be poorly cross-reactive with the commercially available vaccine strains.

A variety of studies have evaluated the impact of vaccination on pre-harvest food safety in cattle.[304] Systematic reviews and meta-analyses have shown that commercial *E. coli* O157:H7 vaccines, targeted against type III secreted proteins or siderophore receptors and porin receptors (SRP) and used in a two- or three-dose regimen, are effective at reducing fecal shedding.[305]

A recent meta-analysis of four randomized control trials that evaluated type III secreted protein-based vaccines estimated efficacy in reducing fecal *E. coli* O157:H7 shedding at 48 percent.[306] A significant decrease in the prevalence of high shedders (by 71.4 percent) has also been reported in response to type III vaccines, even though results were highly variable.[307] Due to their molecular target, type III secretion vaccines might also be effective against non-O157:H7 Shiga toxin-producing *E. coli* even though experimental studies have so far been lacking and would be needed to evaluate potential efficacy.[308]

Another field study performed in a commercial feedlot and not included in previous systematic reviews found that a two-dose regimen of the commercial SRP vaccine (instead of the standard three-dose regime) was 53 percent effective in reducing the prevalence of *E. coli* O157:H7 shedding and reduced the prevalence of high shedders by 77 percent.[309] Notably, vaccination negatively affected average daily gains and feed conversion efficacy.[310] The reason for these negative production impacts of vaccination, which have also been reported in other studies, are not clear but may include the stress of handling the animals during vaccination, the demands on the animal's organism to generate an immune response to the vaccine, or other factors.[311] In addition, labor costs and the actual cost of the vaccine (about $2.50 per dose based on 2011 data)[312] considerably add to the cost of the intervention.

A risk assessment model has quantified the potential public health impact of type III secreted proteins and SRP vaccines on human health, while other risk assessment models have predicted the public health impact of hypothetical vaccines in a variety of situations.[313] The different models have provided fairly consistent results. According to one model, a vaccine that reduces fecal shedding of *E. coli* O157:H7 by 50 percent could reduce human infection by nearly 85 percent if it reduced the highest concentrations shed.[314] Another model estimated that reducing fecal shedding by 80 percent, if applied to all U.S. steers and heifers, would reduce the number of human illnesses associated with *E. coli* O157:H7 in ground beef by almost 60 percent.[315]

Fewer studies have evaluated the efficacy of *Salmonella* vaccines in calves or adult cattle, and results have been variable. A field trial for the commercial *Salmonella* Newport SRP vaccine in feedlot cattle showed no significant effect on the prevalence of fecal shedding.[316] Another study performed in dairy cattle reported a significant decrease in *Salmonella* prevalence in both vaccinated and control groups, but no statistically significant difference between the vaccinated and unvaccinated groups. The authors suggested herd immunity may have contributed to the nonsignificant differences among groups, because vaccination of half of the population with an efficacious vaccine and the resulting immunity may reduce transmission rates sufficiently to protect the unvaccinated animals. This demonstrates the importance of ecologic aspects of *Salmonella* infection on farms and feedlots.[317]

A third study, also done with dairy cows, found evidence that a whole-herd use of an SRP vaccine for *Salmonella* Newport may be useful to control the pathogen in cattle. *Salmonella* prevalence in vaccinated herds equaled 8 percent compared with 37 percent in unvaccinated herds. The study, however, was not originally designed to evaluate this association, and further research is needed to assess the vaccine's efficacy.[318] Under experimental conditions the use of the commercial *Salmonella* Newport SRP vaccine in dairy cattle without clinical symptoms of salmonellosis has led to an increase in milk yield, but the underlying mechanism has so far remained unclear.[319]

Table E-8
Benefits, Limitations, and Data Gaps of Vaccines in Cattle

Benefits	Limitations	Data gaps
Impacts on animal health and production as well as food safety Demonstrated efficacy for *E. coli* O157:H7; efficacy correlated with number of administered doses; some commercial products on the market, others in pipeline Some efficacy for reduction of *Salmonella* fecal shedding Easy to implement in feedlots (efficacy may differ across production settings) Adoption easy to verify Likely more widely acceptable to consumers than some interventions, even though vaccination may be unacceptable to some consumers Impact on environmental shedding	Efficacy differs across pathogens Protection relatively serotype-specific Heterogeneity of effect (depending on measured outcome, sample matrix, number of doses) Some limitations in availability (e.g., conditional licensing) Potential negative impacts on animal performance (e.g., production loss) Potentially relatively high economic cost Potential for immune selection for non-cross-reactive strains	Efficacy for other pathogens and serotypes (e.g., most *Salmonella* serotypes) Efficacy for other outcomes than fecal shedding (e.g., lymph node colonization) Data to evaluate time-period effects Mechanisms underlying potential negative effects of vaccination on animal performance (e.g., stress-related impacts, direct vaccine effects) and differences across vaccines

Biosecurity

Even though few studies have systematically evaluated and quantified the impact of biosecurity practices for pre-harvest food safety in cattle, it is generally considered a prerequisite for food safety as well as animal health.

Table E-9
Benefits, Limitations, and Data Gaps of Biosecurity in Cattle

Benefits	Limitations	Data gaps
Wildlife (e.g., birds) have been shown to shed *E. coli* O157:H7 and other pathogens such as *Campylobacter* Control of wildlife populations has been shown to have some impact Evidence for the correlation between environmental conditions (e.g., pen maintenance) and shedding rates in feedlots	Limited experimental studies demonstrating direct impact on pathogen prevalence and/or concentration USDA Food Safety and Inspection Service and industry guidelines for pre-harvest pathogen controls identify interventions that, even in the absence of a demonstrated impact on prevalence, are certainly beneficial (clean feed and water, self-draining environment, pest and insect control)	Effect may differ by setting; efficacy not always clearly demonstrated in experimental studies Differential impacts across geographic regions, pathogens, management practices

Feed and water

Contaminated feedstuff can be a source of infection for cattle, and can endanger public health.[320] Good feed hygiene is an instrumental prerequisite to pre-harvest food safety.[321]

Several studies have shown that the type of feed itself can have an impact on pre-harvest food safety, even though the underlying mechanism is not completely understood. For example, studies have found that the inclusion of distillers grains (a mash generated as the byproduct of the brewing or biofuel production process) in cattle feed increases the shedding of *E. coli* O157:H7.[322] Other feed types such as cottonseed, clover, corn silage, beet pulp, and barley have shown both positive and negative associations with *E. coli* O157:H7 incidence in cattle. Overall, the data are currently insufficient to determine the impact of these feeds, as well as of grass versus grain diets, on the prevalence and concentration of *E. coli* O157:H7 in feces.[323] Switching cattle from a high-grain diet to a foraging grass diet a couple of days before slaughter might decrease the shedding of *E. coli* O157:H7. Results from experimental studies, however, have been inconsistent, and this practice also results in weight loss, which is disadvantageous to producers.[324]

Water can also be a source of pathogens. Several studies demonstrate that drinking water can be a reservoir for *E. coli* O157:H7 and may help disseminate the pathogen.[325] Chlorination, electrolyzed water, and ozonation are water treatment methods that kill bacteria, but not all of them are currently practical, economical, or effective in reducing the prevalence of pathogens in cattle, and some may render the water unacceptable to the animals.[326] While sunlight and chlorination can reduce *E. coli* O157:H7 in water troughs, sunlight and organic matter such as manure can also reduce the effectiveness of chlorination.[327]

Table E-10

Benefits, Limitations, and Data Gaps of Food and Water for Cattle

Benefits	Limitations	Data gaps
Feed and water are potential vehicles for pathogens, but the impact of stricter hygiene standards is difficult to evaluate; may differ by pathogen, overall pathogen status of the operation Inclusion of brewer's yeast consistently and reproducibly increases risk of shedding for certain pathogens when compared with corn-based diets Shedding rates may differ by crop type (e.g., barley, corn, cotton) and/or forage quality	Use as interventions currently not clear, will likely require understanding of the mode of action or at least more experimental data	Mechanism of action Data for several types of grains and different pathogens

Appendix F: Efficacy of pre-harvest interventions for swine

Note: These findings are based on a review of the literature; particular emphasis is given to relevant opinions provided by the European Food Safety Authority (EFSA). The authors did not convene an expert panel to discuss pre-harvest interventions for swine (however, two of the peer reviewers are veterinarians with considerable expertise in the swine sector), and an expert opinion similar to the EFSA opinions but issued by U.S. agencies was not available.[328]

Prebiotics

Several studies have investigated the impact of prebiotics on pigs' growth performance, but relatively few have evaluated the impact of prebiotics on *Salmonella* shedding in swine; results have been variable.[329] Some studies have generated tentatively encouraging results. One study reported somewhat reduced *Salmonella* Typhimurium shedding after administration of fructooligosaccharide in drinking water, although results were not statistically significant.[330] Another study reported a decreased *Salmonella* shedding prevalence when beta-galactomannan oligosaccharide was included in the diet of fattening pigs.[331] Other researchers demonstrated improvements in anti-*Salmonella* immune responses after inclusion of prebiotics in the diet, but potential impacts on shedding were not evaluated.[332] More studies are needed to better understand if and when prebiotics may be efficient and cost-effective pre-harvest interventions in swine, and which prebiotics and delivery methods may be most appropriate.

> "Unfortunately, to date, no convincing and reproducible results have been obtained in pigs in this respect and further investigations are needed as outlined by (Letellier et al., 2000*)."
>
> EFSA†

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* Ann Letellier et al., "Assessment of Various Treatments to Reduce Carriage of *Salmonella* in Swine," *Canadian Journal of Veterinary Research* 64, no. 1 (2000), https://www.ncbi.nlm.nih.gov/pubmed/10680653?dopt=Abstract.

† European Food Safety Authority, "Scientific Opinion on a Quantitative Microbiological Risk Assessment of *Salmonella* in Slaughter and Breeder Pigs," *EFSA Journal* 8, no. 4 (2010): 1547, http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2010.1547/epdf.

Probiotics

Probiotics are potentially effective at reducing intestinal pathogen colonization of swine. Many of the studies to date, however, have focused on animal pathogens such as *E. coli* strains causing disease in piglets, rather than zoonotic ones (that is, ones that spread from animals to humans), and variable efficacy has been reported.[333] Efficacy may differ by probiotic combination, animal age group, and other management-related factors.[334] One study failed to observe statistically significant impacts of direct-fed microbials administered to late-finishing pigs in feed or drinking water on fecal shedding rates and tissue concentrations.[335] Another study, on the contrary, found significant reductions in fecal shedding and clinical symptoms in weaned pigs fed probiotics in milk when compared to control animals fed milk only.[336]

> In recent years, probiotic bacteria have been considered as an alternative means of reducing pathogen loads in animal breeding and production units."*
>
> István Szabó et al.†

> To be maximally effective, competitive exclusion should be administered before a potential exposure to *Salmonella* spp. Wider studies are needed to fully quantify the effects of competitive exclusion in preventing *Salmonella* infections in pigs."
>
> EFSA‡

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* Paula J. Fedorka-Cray et al., "Mucosal Competitive Exclusion to Reduce *Salmonella* in Swine," *Journal of Food Protection* 62, no. 12 (1999): 1376–80; Kenneth J. Genovese et al., "Competitive Exclusion of *Salmonella* From the Gut of Neonatal and Weaned Pigs," *Journal of Food Protection* 66 (2003): 1353–59.

† European Food Safety Authority, "Scientific Opinion on a Quantitative Microbiological Risk Assessment of *Salmonella* in Slaughter and Breeder Pigs."

‡ European Food Safety Authority, "Opinion of the Scientific Panel on Biological Hazards on the Request From the Commission Related to 'Risk Assessment and Mitigation Options of *Salmonella* in Pig Production,'" *EFSA Journal* 341 (2006): 1–131.

Bacteriocins and colicins

Some colicins have been successful in reducing post-weaning disease in piglets caused by *E. coli* infection, whereas others were not effective.[337] More data are needed to evaluate the efficacy of bacteriocins and colicins as pre-harvest food safety interventions, in particular against *Salmonella* and other zoonotic pathogens.

Antimicrobial drugs

Reports for antimicrobial drug use among pigs have revealed varying effects. There is broad consensus that antimicrobials should not generally be used as a pre-harvest intervention against *Salmonella* in pigs.[338] In fact, a meta-analysis of intervention studies found limited efficacy and potential harmful effects (increased fecal shedding prevalence) associated with tetracycline use, even though results were highly heterogeneous across studies, the number of studies was small, and studies raised quality concerns.[339]

> [A]ntimicrobials should not be used in *Salmonella* control in pig production due to the increased risk of the emergence of antimicrobial-resistant *Salmonella*, which is in line with published EFSA opinions."*
>
> EFSA†

> In pigs, the use of antimicrobials also disrupts the gut flora; it can oppose the growth of certain bacterial populations and thereby facilitate *Salmonella* proliferation."‡
>
> EFSA†

* European Food Safety Authority, "Opinion of the Scientific Panel on Biological Hazards on 'Risk Assessment and Mitigation Options of *Salmonella* in Pig Production'"; European Food Safety Authority, "Scientific Opinion of the Panel on Biological Hazards on a Request from the European Food Safety Authority on Foodborne Antimicrobial Resistance as a Biological Hazard," *EFSA Journal* (2008): 1–87; European Food Safety Authority, "Joint Opinion on Antimicrobial Resistance (AMR) Focused on Zoonotic Infections," *EFSA Journal* 7 (2009).

† European Food Safety Authority, "Scientific Opinion on a Quantitative Microbiological Risk Assessment of *Salmonella* in Slaughter and Breeder Pigs."

‡ Peter J. van der Wolf and N.H.M.T. Peperkamp, "*Salmonella* (Sero)types and Their Resistance Patterns in Pig Faecal and Post-Mortem Samples," *Veterinary Quarterly* 23 (2001): 175–81.

Sodium chlorate

Data on the efficacy of sodium chlorate in swine are currently scarce. A literature review of several on-farm interventions reported that including chlorate in the diet and in the drinking water of swine reduces the population of *Salmonella* and *E. coli* O157:H7.[340] However, more studies, including large field trials on actual commercial establishments, are needed.

Bacteriophages

Experimental studies, primarily relying on artificial challenge with *Salmonella* inoculums prepared by the investigators, have provided tentatively promising results. The approach has also shown positive impacts on pigs' performance parameters, measured as average daily gains.[341] However, more studies are needed, including field studies that directly measure reductions in fecal shedding in finishing pigs under realistic production conditions and after natural infections.

Vaccines

Two systematic reviews of the impact of vaccination on shedding of *Salmonella* in market-weight and younger swine evaluated the scientific literature, including live and inactivated vaccines, and found vaccines effective at reducing prevalence. But the number of available primary studies was small, and there were limitations to the research evaluated, including in suboptimal study design and in reporting.[342] Limited cross-protection across serotypes can be a challenge to vaccine efficacy. A study analyzed cross-protective effects of *Salmonella* vaccines against closely and more distantly related serotypes and found significant impacts on fecal shedding, even though efficacy against more distantly related serotypes tended to be lower than against strains closer to the vaccine strain.[343]

> Vaccines are in limited use in some countries for *Salmonella* control in breeder pigs but may also be used in piglets. Their efficacy in reducing prevalence is not yet fully proven."[*]
>
> EFSA[†]

> Vaccination alone cannot eliminate *Salmonella* spp. from a herd, and whether vaccination is a suitable option in a control programme or not, depends on the aim of control programme (reduction or eradication), prevalence of *Salmonella*, serovars involved, detection methods used and cost-benefit."
>
> EFSA[‡]

[*] Thomas N. Denagamage et al., "Efficacy of Vaccination to Reduce *Salmonella* Prevalence in Live and Slaughtered Swine: A Systematic Review of Literature From 1979 to 2007," *Foodborne Pathogens and Diseases* 4, no. 4 (Nov. 2007): 539-549, doi:10.1089/fpd.2007.0013.

[†] European Food Safety Authority, "Scientific Opinion on a Quantitative Microbiological Risk Assessment of *Salmonella* in Slaughter and Breeder Pigs."

[‡] European Food Safety Authority, "Opinion of the Scientific Panel on Biological Hazards on the Request from the Commission Related to 'Risk Assessment and Mitigation Options of *Salmonella* in Pig Production.'"

General biosecurity

As with cattle, biosecurity is a prerequisite for pre-harvest food safety in swine. Few studies have directly assessed the impact of individual biosecurity measures. The few available studies are highly diverse, largely precluding formal assessments through meta-analysis.[344] However, data from European *Salmonella* surveillance programs provide evidence that poor biosecurity in swine herds is associated with a higher probability of testing *Salmonella*-positive.[345]

Feed and water

Contaminated feed can clearly be a source of pathogens.[346] In fact, some researchers have attributed observed low incidence of *Salmonella* in cattle and swine in several European countries to the strict animal feed hygiene controls followed.[347]

The type of feed itself may also affect susceptibility to *Salmonella* infections. Two systematic reviews have found that feeding nonpelletized meal to swine yielded a protective effect against *Salmonella*. However, the data were limited, and well-designed controlled studies would be necessary to substantiate these findings.[348] Wet feed was also associated with reductions in *Salmonella* shedding,[349] but a systematic review could not detect a significant effect because the number of available high-quality studies was insufficient.[350] The underlying mechanisms of action have remained unclear, although it has been suggested for broiler chickens that feed particle size itself affects gut transit times and resulting exposure to gastric acids, causing the observed effects.[351]

Contrary to the situation for poultry, the effectiveness of feed acidification as an intervention for the control of *Salmonella* in swine has not been demonstrated. Studies to date have yielded inconsistent results, likely because of variation among farms using the method as well as regional differences.[352]

> Acidification of feed was put forward as a way to control *Salmonella* ...
>
> "The acidified drinking water (pH = 3.6-4.0) decreased neither *Salmonella* shedding at the slaughterhouse, nor the level of carcass contamination."
>
> EFSA[*]

> [F]eeding pelleted feed was associated with an increased risk of seropositivity for *Salmonella* at slaughter compared to feeding non pelleted feed and that wet feed and the use of whey were associated with reduced risk for seropositivity.[†]
>
> "Fermenting feed or using fermented feed components (fermented liquid feed – FLF) used as a wet feeding system is found to have a *Salmonella* reducing effect."[‡]
>
> EFSA[§]

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[*] European Food Safety Authority, "Scientific Opinion on a Quantitative Microbiological Risk Assessment of *Salmonella* in Slaughter and Breeder Pigs."

[†] Danilo Lo Fo Wong and Tine Hald, "*Salmonella* in Pork (SALINPORK): Pre-Harvest and Harvest Control Options Based on Epidemiologic, Diagnostic, and Economic Research" (2000): 132–55, http://s3.amazonaws.com/zanran_storage/www.dfvf.dk/ContentPages/51870756.pdf.

[‡] Peter H. Brooks et al., "Fermented Liquid Feed (FLF) Can Reduce the Transfer and Incidence of *Salmonella* in Pigs," *International Symposium on the Epidemiology and Control of Foodborne Pathogens in Pork* (2003): 21–27; Peter J. van der Wolf et al., "*Salmonella* Infections in Finishing Pigs in the Netherlands: Bacteriological Herd Prevalence, Serogroup and Antibiotic Resistance of Isolates and Risk Factors for Infection," *Veterinary Microbiology* 67 (1999): 263–75; Peter J. van der Wolf et al., "Risk Factors for *Salmonella* Infections in Finishing Pigs in the Netherlands," Symposium of the International Society for Animal Hygiene (2000): 238–87; Peter J. van der Wolf et al., "A Longitudinal Study of *Salmonella enterica* Infections in High- and Low-Seroprevalence Finishing Swine Herds in the Netherlands," *Veterinary Quarterly* 23 (2001): 116–21.

[§] European Food Safety Authority, "Opinion of the Scientific Panel on Biological Hazards on the Request From the Commission Related to 'Risk Assessment and Mitigation Options of *Salmonella* in Pig Production.'"

Appendix G: The value of monitoring and testing programs

Identifying and managing pathogen-positive animals, herds, or flocks are common control strategies adopted by several countries in Europe, often in combination with other interventions. Having this information allows for management decisions such as destruction or logistic slaughter, which can prevent or reduce contamination of the food supply. A fundamental question in designing any monitoring or testing program is whether to rely on serology or microbiological testing. Serology measures the immune response to infection, whereas microbiological testing measures the presence of the pathogen of interest. Both can result in false positive and false negative results. Because animals require several days to mount immune responses to infection, new infections are typically not immediately detectable by serology. Animals may also remain seropositive after the infection has been cleared. In some cases immune responses to vaccination may not be differentiable from natural infections, even though DIVA strategies can overcome that problem. (See Appendix B for more on the mechanism of action for DIVA vaccines.)

However, serology testing may be beneficial for *Salmonella*. While some scientists have suggested that serotyping may overestimate the public health risk because seropositive animals may not be actively shedding *Salmonella*, others emphasize that serotyping is important to understanding the spread of disease through the food chain, in particular because animals often shed *Salmonella* intermittently—when stressed during transport and lairage, for instance.[353]

The value of testing may depend on the stage of a pathogen control program. A mathematical model analyzing the Danish *Salmonella* control program for swine found that, with the exception of the first four years after implementation, the on-farm surveillance program did little to reduce the number of positive carcasses and pork-attributed human cases. The study further suggested that post-harvest interventions (that is, carcass decontamination) may be a more effective strategy to improve public health.[354]

Sample design and test selection are critically important when developing a pathogen-surveillance program. Testing methods and strategies need to be selected considering costs and the ability of the test to accurately identify a positive or negative animal, flock, or herd. This can become particularly important when dealing with extremely rare diseases because even the best test has some risk of falsely detecting a positive, and the fraction of these false-positive results increases drastically as disease prevalence in a test population decreases. Test performance is equally important to keep in mind when dealing with suboptimal tests. Some pathogens, such as *E. coli* O157:H7 and *Salmonella*, can be shed intermittently, which necessarily reduces the ability of a microbial test to correctly detect infected (but not currently shedding) animals and limits the benefit of surveillance.[355]

Appendix H: Overseas successes with pre-harvest interventions

A number of countries have instituted successful, comprehensive food safety control programs that include a strong pre-harvest component. The programs are often partnerships between government and the livestock industry—initiated using government appropriations and sustained with industry dollars.

Sweden, Finland, and Norway

Sweden, Finland, and Norway have adopted aggressive measures to control *Salmonella* in poultry production. In Sweden, voluntary control programs started in 1970 but became mandatory in 1984 for poultry meat and in 1994 for laying hens.[356] These measures include heat-treating feed before delivery to a poultry farm. Biosecurity measures are required on the farm, including removing litter[357] between consecutive flocks. All imported birds, which are day-old "grandparents," are quarantined for 15 days and tested for *Salmonella* four times during this period. Further monitoring occurs throughout critical production points. All positive flocks are destroyed, and producers are compensated for their losses through insurance. Since 1995, the incidence of food products with *Salmonella* in Sweden is less than 0.1 percent.[358]

In 1991, Sweden started a *Campylobacter* program focused on hygiene measures on the farm, and by 2006 the number of *Campylobacter*-positive flocks had decreased from 50 percent to 10 percent. Decreases in the prevalence of *Campylobacter* in poultry products, however, have not been seen, indicating that contamination is occurring somewhere in the post-harvest process.

Finland and Norway have adopted programs similar to Sweden's.[359] Finland requires extensive *Salmonella* testing, and contaminated animals must be handled separately. The use of their products is restricted, and potential sources of contamination have to be investigated.[360] As a result of these programs, the prevalence of *Salmonella* in Finnish and Norwegian poultry meat is less than 1 percent. These countries have also experienced improvements in public health with fewer human salmonellosis cases.[361]

Finland compared the costs and benefits of its program, which focuses on all *Salmonella* serotypes and includes commercial broilers, with the European Union directive 92/117/EC that only required the control of *S.* Typhimurium and *S. enteritidis* in breeder flocks. This study found that, while its comprehensive program was seven times more costly than that of the EU directive, it generated 33 times more savings in public health costs by reducing all *Salmonella* cases.[362]

In addition to the public health benefits, these three countries are granted special guarantees by the EU that allow them to limit imports of certain meat, eggs, and some live animals. These guarantees allow Sweden, Finland, and Norway to accept only imported products that have tested negative for *Salmonella* control.[363]

Denmark

Denmark has a comprehensive surveillance program that includes all parts of the poultry production chain. Increased hygiene requirements at the farm include removal of all organic material between flocks, regular thorough cleaning and disinfection of the poultry house, and a "resting period" of 10 to 14 days after the houses are empty before a new flock is introduced.[364] *Salmonella*-positive flocks are slaughtered separately, and the meat from these flocks must be cooked before it is sold. Additionally, meat from *Salmonella*-negative flocks can be labeled as "*Salmonella*-free." Broiler-breeding flocks that are *Salmonella*-positive are destroyed.

Pigs are also tested regularly, and animals from herds with high levels of *Salmonella* are slaughtered under special hygiene conditions. Farmers receive lower payments for pigs from *Salmonella*-positive herds than from those with low levels of *Salmonella*.[365]

Denmark estimates that *Salmonella* infections in the population from 1994 to 2005 have been reduced by up to 600,000 and that 600 premature human deaths may have been avoided.[366] In addition:

- Chicken-associated salmonellosis incidence (cases per 100,000 inhabitants) decreased by more than 95 percent, from 30.8 in 1988 to 0.5 in 2001.
- Pork-associated salmonellosis incidence decreased by more than 85 percent, from 22.0 in 1993 to 3.0 in 2001.
- Egg-associated salmonellosis incidence has been reduced by nearly 75 percent, from 57.7 in 1997 to 15.5 in 2001.[367]
- In 2001, the total cost of annual *Salmonella* control in Denmark was estimated at US$14.1 million (7.5 cents per kilogram for pork and 2 cents per kilogram for broilers and eggs) and was paid mainly by industry. That year, Danish society saved up to $25.5 million by avoiding health-related costs and reducing lost productivity associated with *Salmonella* infections.[368]

Iceland

To control a *Campylobacter* epidemic that began in 1999, the Icelandic government employed a series of measures, including a mandatory surveillance program in which broilers and other poultry flocks were tested systematically before processing. Birds were not allowed to be slaughtered before their test results were available. In addition, training on biosecurity measures was provided to producers, and the practice of partial slaughter (thinning of the flock) was stopped to avoid the risk of introduction to the flock. But one of the most significant measures required that all poultry products from confirmed *Campylobacter*-positive flocks be frozen before retail because freezing significantly decreases the levels of *Campylobacter*. Because frozen poultry is cheaper than fresh poultry, producers have a strong incentive to strive for *Campylobacter*-free flocks. As a result of this program, the rate of *Campylobacter* infections in Iceland decreased from 62 per 100,000 population to 21 per 100,000 population.[369]

The European Union

In the 1990s, the European Union set monitoring standards for *Salmonella* and established controls for *S. enteritidis* and *S.* Typhimurium in breeding flocks and feed.[370] In 2003, European directive EC 2160/2003 extended the program, which required member countries to create national control programs (with effective dates based on species) that cover feed and primary production of animals as well as processing and preparation of animal food products.[371] The EU also introduced requirements for testing and sampling of zoonoses and zoonotic pathogens at several points, including *Salmonella* at breeding, primary production, and slaughter for swine herds. The program now focuses on poultry, eggs, and pigs, and covers all *Salmonella* serotypes with public health significance. All control programs must be submitted to the European Commission for evaluation.[372]

Although member states must have a national control program for *Salmonella*, there are no sanctions if a member state does not reach the stated targets for reducing illnesses.[373] Still, the number of salmonellosis cases in the EU is in decline. Between 2012 and 2013, there was a 7.9 percent decrease, with an overall declining trend in the five-year period between 2009 and 2013, although this was not statistically significant when analyzed by month.[374]

Endnotes

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2 Michael B. Batz, Sandra Hoffmann, and J. Glenn Morris, "Ranking the Disease Burden of 14 Pathogens in Food Sources in the United States Using Attribution Data from Outbreak Investigations and Expert Elicitation," *Journal of Food Protection* 75, no. 7 (2012).

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5 Batz, Hoffmann, and Morris, "Ranking the Disease Burden of 14 Pathogens in Food Sources in the United States Using Attribution Data From Outbreak Investigations and Expert Elicitation."

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