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REVIEW
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A Commentary on *Salmonella* From a Pre-Harvest Perspective

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Salmonella occurs in all the major meat producing livestock species (ruminants, swine and poultry), most often residing within the gastrointestinal tract asymptomatically. While considerable success has been achieved post-harvest, the design of effective pre-harvest interventions to control *Salmonella* has lagged. A simplistic view of the extremely complex host/pathogen interaction suggests that the pathogen has a vested interest in not causing illness or death to the host. The former would initiate an immune response from the host and/or the application of therapeutic antibacterial agents, while the latter would require finding another suitable host. Due to the widespread prevalence of *Salmonella* within livestock and poultry, and the relatively few salmonellosis cases in comparison, it appears, and is supported by new research, that *Salmonella* has developed methods to avoid detection by the animal's immune system and live essentially as a commensal organism within the gastrointestinal tract of the animal. Yet, for reasons that are not fully understood, this "commensal" *Salmonella* does on occasion become virulent, in young and mature animals alike. Indeed, these researchers have documented *Salmonella* carriage throughout the year in cattle, but only rarely, if at all, was salmonellosis observed. Further, evaluation of *Salmonella* isolates (serotype and antimicrobial resistance patterns) from sick and healthy cattle failed to explain that while *Salmonella* was present in the majority of cattle sampled on that farm, only a few developed salmonellosis. Virulence, as well as multi-drug resistance, in both livestock and humans appears to cluster within a few serotypes. As a result, petitions are circulating calling for the labeling of some *Salmonella* serotypes as adulterants, as was done with *Escherichia coli* O157:H7 and other enterohemorrhagic *E. coli* strains. Regulators are considering approaching the *Salmonella* problem by serotype, such as focusing specifically on the top 10 reported serotypes causing human illness. Herein, the authors will discuss the many challenges of controlling *Salmonella* pre-harvest, reflecting on the significant research portfolio that has been generated over the last 25 years, as well as challenging existing paradigms surrounding this pathogen and the experimental methods used to further our understanding of *Salmonella* and/or evaluate methods of control.

Keywords: *Salmonella*, livestock, poultry, pre-harvest, gut health

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INTRODUCTION

Salmonella, a foodborne pathogen of concern from a human health standpoint, commonly infects most all livestock and poultry species. Indeed, the presence of *Salmonella* within beef and dairy cattle, poultry (broilers, layers and turkeys) as well as swine, at most every stage of production is well documented (Chlebicz and Slizewska, 2018). That said, many outbreaks are also a result of eating contaminated vegetables and other non-meat foods (McEntire et al., 2014). Recently, due to the number of human outbreaks of salmonellosis linked to the consumption of meat protein, a petition has been produced calling for the labeling of *Salmonella* as an adulterant, with a zero-tolerance policy, as has been implemented to reduce *E. coli* O157:H7 and the other "Big Six" enterohemorrhagic *E. coli* strains. Whether or not this petition will provide impetus that leads to the labeling of *Salmonella* as an adulterant remains to be seen, however, many expect *Salmonella* to be declared an adulterant in some form or another, at some point. Considering the widespread prevalence of *Salmonella* within meat-producing animals, if labeling of *Salmonella* as an adulterant in some form or fashion does happen, it will present a significant challenge for the meat industry.

To address this challenge, considerable research effort has been expended to further our understanding of *Salmonella* within the livestock production environments and within and among animals, as well as toward the development and testing of novel pre-harvest intervention strategies. At slaughter, significant progress has been made in post-harvest interventions that limit the transfer of pathogens from the hide to the surface of the carcass (Koohmaraie et al., 2005; Wheeler et al., 2014). However, despite the progress that has been made on the control of pathogens on the surface of the carcass, progress towards achieving Healthy People 2010 and 2020 *Salmonella* objectives have fallen short (Healthy People, 2020). To add to the challenge of controlling *Salmonella* in beef products, it was discovered about a decade ago that this pathogen often resides within the peripheral lymph nodes (PLN) (Arthur et al., 2008). These nodes, encased within adipose tissue are impervious to in-plant interventions, and unless removed by trimming, constitute a source of *Salmonella* contamination in trim and ground beef (Arthur et al., 2008; Li et al., 2015). Hence, the development of effective pre-harvest interventions is imperative to addressing *Salmonella* in the animal protein sector.

Ten to 15 years ago, food safety sessions were held at most scientific meetings related to animal agriculture and the number of scientists engaging in pre-harvest food safety research was substantial, with significant competition for extramural funding. Fast forward to today, the number of researchers has declined dramatically, and the efforts of many having been partially or wholly redirected to new areas of research. Why? The lack of novel hypotheses could be one explanation. Frustration with the pathogen itself, that once appeared to follow certain paradigms, but more recently does not, could be another. Most that have conducted considerable research with *Salmonella* will likely attest to its ability to be unpredictable. The inability to quickly make a splash and develop that successful intervention could account for some fallout. Fortunately, there remain many quality researchers that have not been deterred by the challenge *Salmonella* poses and these authors are confident that successful pre-harvest interventions will be developed.

In the book "*The Art of War*", it is said: "If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle." Could this explain, at least partially, the lack of success in the development of effective pre-harvest intervention strategies for *Salmonella*? How well do we know this enemy called *Salmonella*?

SALMONELLA – WHAT DO WE REALLY KNOW?

The purpose of this discussion is not to present a thorough literature review of all that has been done in livestock and poultry, but rather, it is a synopsis of what, in the author's opinions, are key findings and a discussion around where *Salmonella* research has been (primarily cattle focused) and more importantly where it could, or should, progress. *Salmonella* is a gram-negative bacterium, with 2,800 plus variations, or serotypes, found in the gastrointestinal tract (GIT) of livestock and poultry, to such a degree that they are considered reservoirs for this pathogen. In general, *Salmonella* is more prevalent in the summer and early fall months compared to winter and spring. Research has indicated it is more often found in southern versus northern latitudes (Webb et al., 2017; Nickelson et al., 2019). Yet, with increasing frequency, observations are being reported that challenge these generally accepted paradigms. Is *Salmonella* adapting to new environments once thought less than ideal? The progression of *Salmonella* northward in livestock operations in the United States and Canada would suggest this may be the case.

Salmonella can and does cause salmonellosis, however more often than not, it resides asymptomatically in the GIT without causing any apparent negative effects to the host. Indeed, if one considers the host-pathogen relationship, the pathogen has a vested interest in keeping its host alive. Causing illness or death results in activation of the immune system, possible administration of antimicrobials, and ultimately the loss of a suitable host, thereby threatening the survival of the pathogen. Considering the widespread abundance of *Salmonella* and the relatively few cases of salmonellosis, it appears as though *Salmonella* has found a way to live harmoniously within livestock and poultry hosts.

Why doesn't the host's immune system recognize *Salmonella* as a pathogen and seek to rid the body of it? Dairy cattle in the southwestern United States have been reported to carry a significant load of *Salmonella* within their GIT and shed the pathogen in their feces (Fitzgerald et al., 2003; Edrington et al., 2004; Edrington et al., 2008a; Edrington et al., 2008b). In dairy cattle, young calves are the most susceptible to salmonellosis, while most of the older animals appear relatively immune, yet *Salmonella* resides with the GIT, often year-round. There are

exceptions of course, which will be discussed below. Research seeking to understand when a young dairy calf first acquires *Salmonella* reported fecal shedding in dairy calves at one week of age (Edrington et al., 2012) and subsequent research (unpublished data) found *Salmonella* in the feces of calves at one day of age. Researchers hypothesized that while these young calves could have acquired *Salmonella* during the birthing process or shortly thereafter, the data suggested that calves may in fact be born with *Salmonella*. Research testing this hypothesis (Hanson et al., 2015) demonstrated vertical transmission of *Salmonella* from dam to calf, finding *Salmonella* not only in several segments of the GIT, but also in peripheral and mesenteric lymph nodes. This then begs the questions, if a calf is infected with *Salmonella* from its dam, will its immune system recognize it as a threat upon subsequent, repeated exposure? Is the calf's immune system adequately developed, such that it is capable of pathogen memory and recognition at this stage of its life? Is this why salmonellosis in young calves 1-2 weeks of age can be particularly severe? Does previous exposure from the dam result in partial or no immune response? Could this continuum of exposure (dam to calf) help explain, at least in part, why *Salmonella* appears to thrive in the dairy environment?

In these same dairies, salmonellosis does occur in mature lactating animals, generally in the fall of the year. Specifically, when large temperature swings are observed (observational data shared by dairymen in the SW U.S.). Research seeking to better understand the dynamics of these outbreaks first examined *Salmonella* isolates from sick and healthy cows on a dairy experiencing a salmonellosis outbreak, and second evaluated *Salmonella* monthly in the same set of lactating dairy cows over a year's time (Edrington et al., 2008b). No differences were noted in *Salmonella* serogroup, serotype, genetics, or antimicrobial resistance (AMR) patterns between isolates obtained from sick and healthy cows. During the second year of the study, 30 cows were sampled monthly and while *Salmonella* was routinely cultured, and highly variable from month to month, from both the cows and the environment, no salmonellosis outbreak occurred. Good news for the farmer, but potentially unfortunate for science that seeks to understand these outbreaks. So why does a mature animal that carries *Salmonella* within its GIT all year, break with salmonellosis on some occasions, but not others? Why do only some animals within a pen on a dairy experience salmonellosis, while other pen mates do not? Virulence has often been associated, with a few serotypes (Typhimurium, Dublin, Newport, Infantis, and others) that are often multi-drug resistant (MDR). Yet in the study above, no differences in serotype or AMR profiles were noted among sick and healthy animals (Edrington et al., 2008b). Does concentration play a role? Logically, this makes sense. Unfortunately, concentrations of *Salmonella* were not determined in the above work nor are there any reports to the author's knowledge that support the idea of a concentration threshold being exceeded that initiates disease. What about MDR mentioned above? Strains associated with animal salmonellosis outbreaks are typically MDR, with the exception noted above (Edrington et al., 2008b). Does acquisition of resistance also convey virulence? Research that examined the incidence of MDR *Salmonella* on dairies in the southwestern US, reported that MDR *Salmonella* strains were most often found in young calves, pre-weaning, and cows in the hospital pen and their prevalence was low, in comparison to overall *Salmonella* prevalence (Edrington et al., 2008a). The researchers hypothesized that the MDR strains were only able to thrive in an animal with either an immature (calves) or an altered (sick pen cows) gut microflora that allowed for the MDR strains to thrive, whereas in a normal, healthy microflora, they do not compete well due to the physical burden of carrying MDR. That said, young calves and animals in the hospital pen are those most likely to receive antimicrobial therapy, which could explain in part the reported observations. If virulence is associated with MDR, and taking the observations discussed above in which MDR *Salmonella* were most often found in animals with a disturbed or immature GIT microbiome, quite possibly the key to preventing salmonellosis lies in simply maintaining a healthy gut. Unfortunately, the salmonellosis "trigger" remains to be elucidated. What then causes asymptomatic carriage to progress to salmonellosis? And why if examining *Salmonella* from a pre-harvest perspective, does this even matter?

Stress and *Salmonella*

Stress has long been associated with, or implied to cause, an increased pathogen carriage and/or fecal shedding. In theory, this makes considerable sense. Stress may disrupt normal eating patterns and subsequently, the GIT microflora. Further, hormones often associated with stress, catecholamines, are reported to be integral in bacterial quorum sensing utilized by gram negative bacteria to regulate populations (Lyte et al., 1996; Sperandio et al., 2003). Stress may open the tight junctions within the gut, allowing bacteria to escape the gut lumen and cause other disruptions to the intestinal epithelium, allowing for the progression from asymptomatic carriage to disease state. The research above citing a seasonality to salmonellosis outbreaks that consisted of unusual temperature increases following cooler weather, suggests that disruptions in feed intake (due to heat stress) that subsequently negatively impact GIT homeostasis could trigger the event. Do then, stressful events of the same or lesser magnitude influence the *Salmonella* burden within an animal? Perhaps stress increases the incidence of super-shedders, those animals shedding at levels of 3 log or greater, through the catecholamine quorum sensing mentioned above. Could the stress event open tight junctions and thereby allow for the escape of *Salmonella* from the GIT, leading to its subsequent uptake by PLNs? All of these scenarios could play a role in *Salmonella* carriage and some are currently being investigated.

The Immune System

As *Salmonella* can and does cause disease, could an intervention that supports an animal's immune system provide a pre-harvest benefit as indicated by a reduced *Salmonella* burden? In theory it should. Considerable research has explored the use of vaccines as a pre-harvest mitigation tool with mixed results. A comparison of dairy cow herds utilizing a *Salmonella* vaccine found lower

fecal prevalence compared to herds that did not vaccinate (Loneragan et al., 2012) while others reported no vaccine effect on the fecal shedding of *Salmonella* in sub-clinically infected dairy cows (Heider et al., 2008; Hermesch et al., 2008). Research examining the effect of vaccination on *Salmonella* carriage in the PLN, reported limited reductions in experimentally-infected animals (Edrington et al., 2013a; Edrington et al., 2020) and no benefit in naturally-infected feedlot cattle in a commercial feedlot (Cernicchiaro et al., 2016).

As stated above, the vast majority of livestock and poultry carry *Salmonella* asymptomatically, or what appears to be asymptomatically, as there are no visibly negative impacts to health or production. That being the case, it would appear that *Salmonella* has either learned how to avoid detection by the immune system, disguising itself as a non-threatening commensal, or is simply recognized as a commensal organism. Interesting new research is exploring this scenario in poultry and supports the idea that *Salmonella* has learned how to circumvent the immune system (Redweik et al., 2021). Specifically, this research suggests that *Salmonella* manipulates the gut-brain axis to alter the immunometabolic/neuroimmune phenotype in the cecum, allowing for its persistence. Further, enteric pathogens have developed strategies to sense neurochemical molecules to regulate their virulence in the GIT and specific to poultry, *Salmonella* has a selection of traits that act as anti-virulence strategies (Mike Kogut, personal communication; Redweik et al., 2021). Fascinating research helping to explain why this bacterium can reside successfully in poultry, and potentially why *Salmonella* can alternate between a commensal and a pathogen in cattle.

Alternately, consider the vertical transmission discussed above from dam to calf. Does early exposure to *Salmonella*, *in utero*, prevent its recognition as a pathogen when that animal is exposed later in life? What about the environment? *Salmonella* is found throughout livestock and poultry production facilities. Does the constant infection and reinfection pressure, without causing disease, desensitize the immune system over time? That said, if the GIT of livestock and poultry is a preferred location for *Salmonella*, and the environmental exposure and potential for continual reinfection so high, why don't all of the animals within a farm, or pen, or poultry barn have *Salmonella*? Perhaps they do, but sampling procedures or culture techniques fail to detect *Salmonella* with complete accuracy. While these researchers have seen the incidence of fecal shedding of *Salmonella* in cattle reach near 100% on many occasions, more often than not, prevalence is far less. Repeated sampling of the same individual animals has demonstrated significant variation in shedding. Naturally this could be a function of the sample collected, timing of the collection or other factors, and consider fecal collections alone are insufficient to determine if an animal is truly *Salmonella* negative. The data certainly suggests that no two animals are equal in their susceptibility to *Salmonella* colonization. If in fact true, and not an artifact of sample collection bias, then could this be due to immune system recognition in those *Salmonella* "negative" animals. Activation of the immune system requires energy. Continual reinfection with *Salmonella*, if followed by a subsequent immune response, would be expected over time to divert energy from gain, which then may be reflected in performance of those animals. Yet there is nothing to indicate that this is the case. Perhaps immune enhancement would be of benefit. Or quite possibly there are other explanations yet to be uncovered. Perhaps the GIT microbiome is less hospitable in those animals that appear to be *Salmonella* negative.

Gut Health

Interesting how research efforts/ideas cycle and once again gut health is at the forefront, and with good reason. Research into the GIT and in particular, the microflora, has accelerated over the past few years with new technology allowing for new discoveries. Intriguing data is demonstrating the vast role the microflora plays in maintaining homeostasis, not only in the GIT tract, but throughout the body, and the disruptions that occur when that homeostasis is challenged. Should this be the new frontier for pathogen research?

The evolution of livestock and poultry nutrition has been tremendous, with diets fine-tuned for maximum growth and/or production while maintaining animal health and well-being. Coupled with genetic improvements and broilers reaching market age earlier, egg and milk production has increased and time to slaughter for feedlot cattle has decreased. Has this impacted *Salmonella* and its prevalence in livestock and poultry? Quite possibly, however there is insignificant data to verify accurately. That said there is research that may provide a clue.

Salmonella is found at a much lower rate in beef and dairy cattle on pasture than in confinement feeding operations. Likewise, *Salmonella* prevalence was lower in growing heifers and dry cows than lactating dairy cows within a dairy (Edrington et al., 2008a). As environment and animal density are the same for these different classes of dairy cattle, perhaps the different rations provide an explanation. Or revisiting the stress hypothesis, perhaps the stress of parturition, initiating lactation and the negative energy balance experienced by cows in early lactation offer answers. Comparisons were made to determine the effect of heat stress, parity, lactation status, and stage of lactation (Fitzgerald et al., 2003). In that research, no effects of factors were observed for *Salmonella* prevalence with the exception of stage of lactation, where significantly more cows < 60 days in milk (DIM) shed *Salmonella* than those > 60 DIM (Fitzgerald et al., 2003). A second study examining the effect of heat stress and stage of lactation (<60 or >150 DIM) reported no difference in fecal *Salmonella* prevalence due to heat stress with nearly 100% of the cows positive, while shedding tended to be higher in the early lactation cows in the first replicate and in the second replicate higher in the late lactation animals. Perhaps dairy cows in early lactation and in negative energy balance shed more *Salmonella*, however research results are inconclusive and largely highlight the variability in *Salmonella* shedding among animals and the difficulty in teasing out meaningful information.

Has the evolution of livestock and poultry diets modified the GIT such that *Salmonella* now finds it much more hospitable? Even subtle dietary changes can impact the gut microflora,

eliminating or creating competition among species. Beyond the microflora, what role does the health and integrity of the gastrointestinal epithelium play in pathogen prevalence. Liver abscesses in feedlot cattle are generally attributed to bacteria escaping the rumen due to damage to the epithelium, a result of high concentrate inclusion in the diet. There is now interest in the hindgut and what role that may play in the etiology of liver abscesses. Conventional wisdom suggests that *Salmonella* within the PLN is of gut origin, as the bovine GIT is a reservoir for the bacterium. Research has clearly demonstrated that *Salmonella* on the hide of the animal can enter through a wound, such as a fly bite, and will be acquired by the PLN (Edrington et al., 2013b; Edrington et al., 2016; Olafson et al., 2016). That said, the importance of GIT *Salmonella* to the overall contribution to *Salmonella* within these PLNs cannot be dismissed and likely is a large contributor. Recent work, published in this journal issue, examined *Salmonella* with the PLN by different cattle type and reported that cull dairy cows and feedlot animals had the greatest prevalence of *Salmonella* positive PLN, while cull beef cows and grass-fed beef had much lower prevalence (Wottlin et al., 2022). Results suggest either a correlation to animal density, feedstuffs, or both. Not surprisingly, gut health appears to play a significant role in relation to carriage of *Salmonella* within the gut of livestock and poultry, delineating those exact mechanisms will be a challenge.

WHERE DO WE GO FROM HERE?

Design and Evaluation of Interventions

The discovery and implementation of effective pre-harvest interventions has the potential to dramatically impact the safety of animal protein products. Many potential interventions have been examined, most showing limited to no success in reducing *Salmonella* in the live animal. In general, interventions are examined *in vitro*, and if results are promising, small scale animal studies are conducted, most often utilizing experimental challenge models. Success there will then direct the research to larger scale studies, often in commercial production settings. There are problems with this general approach that may potentially exclude promising interventions, or not provide for their proper evaluation.

First, the type of experimentation should match the hypothesized mode of action (MOA) of the intervention. A one size fits all approach like mentioned above will not allow for adequate evaluation of that intervention. For example, if the MOA is a direct killing effect, then *in vitro* screening followed by experimental challenge studies may be a proper evaluation. However, if the MOA involves manipulation of the gut microbiome, such as a direct fed microbial, then *in vitro* methods, even with mixed cultures that do not allow for the complexity of the gut to be included are unlikely to provide proper evaluation. Experimental challenge studies likewise need to be carefully considered. These studies typically involve the dosing of animals with a significant concentration of *Salmonella*, followed by the monitoring of fecal shedding up to a point where necropsy of the animal may be conducted. Large doses are required as small, "more real-world" doses typically are hard to detect following challenge. The result is a measure of how fast the challenge strain washes out of the GIT, unless sufficient time is allowed for the challenge strain to establish with the competing microflora, which more often than not, fails to occur. Another issue with challenge studies involves the animal's response to the challenge itself. Does the administration of millions of *Salmonella*, in a single dose initiate an immune response? This is likely to occur. Does natural exposure to small amounts of *Salmonella* over time produce an immune response? This is unlikely, or at least to a different degree. Recent research reported significant differences in the phosphorylation state of the immune response peptides between naturally- and experimentally-infected cattle, suggesting that the immune system is activated in a significantly different manner (Arsenault et al., 2022). Hence, the use of experimental challenge studies and the interpretation of the data generated must be done carefully with consideration of the protocol itself and the animal response. The optimum test of any intervention will be in a commercial production setting, with naturally-infected animals. Therefore, starting there and eliminating the pre-testing that may or may not be of value may be the correct, or more practical, approach.

Chasing Serotypes and Other Follies

Considerable effort and expense have been devoted to examination of *Salmonella* serotype to include research conducted by these authors. With some 2,800 serotypes identified and the significant prevalence of *Salmonella*, this can be a tedious, sometimes complex, and costly process. After characterization of thousands upon thousands of isolates, has this data improved our ability to reduce *Salmonella* in the animal? Yes, there are serotype specific interventions that have shown benefit against a particular serotype (Newport for example). But overall, the benefit to the overall *Salmonella* problem is negligible at best. The challenge is serotypes shift, and they are often found in multiples. While common serotypes may be dominant, research has demonstrated that serotypes change over time within populations of animals. Examination of *Salmonella* isolates in dairy cattle on four neighboring farms reported that serotype and serotype prevalence changed by season on three of the four farms with a total of 22 different serotypes identified (Edrington et al., 2004). Further research demonstrated serotypes change from month to month within individual dairy cows and further documented five different serotypes within a single fecal sample, in which five isolates were examined (Edrington et al., 2008b). How many isolates must be examined to accurately determine serotype prevalence in an animal, or on a farm? Similar data has been generated in other species and highlight the challenge of addressing the *Salmonella* problem by serotype. Furthermore, culture methodology may influence serotype recovery and this should be taken into consideration.

Further Characterization of Isolates and Whole Genome Sequencing

Considerable research has sought to further examine *Salmonella* isolates obtained from clinical cases of salmonellosis as well as healthy animals, the value of which has largely yet to be determined. Are some species of *Salmonella* more virulent,

more likely to escape the GIT and become systemic, or end up in a PLN? It appears so.

Whole-genome sequencing has been employed extensively over the past decade and while useful in source tracking and the identification of the source of outbreaks, the remaining value seems largely tied to the support of litigation efforts. The challenge then becomes, can a specific pre-harvest intervention be designed around this knowledge, and if so, is this a worthwhile endeavor? Based on the diversity of *Salmonella* serotypes discussed briefly above and the generally accepted idea that if you remove one, another will take its place, then does further characterization of one particular isolate, or isolates, help with the design of interventions that need to target all *Salmonella* strains?

CONCLUSION

Where do we go from here? A thorough review of the literature regarding pre-harvest food safety research for those entering this research arena, as well as continual monitoring of new research is certainly required. Unfortunately, this does not always happen as some current research has reported old findings as new. With a solid foundation of what has been done, then the identification of the key knowledge gaps will drive the subsequent research ideas. For instance, ceca *Salmonella* is not the appropriate metric for evaluation of pre-harvest interventions designed to address *Salmonella* in ground turkey. What is? Another example: does fecal shedding of *Salmonella* correlate strongly enough to the carriage of *Salmonella* within the PLN of cattle, such that it can be used as an indicator for the latter? Answering both of these questions will further facilitate the evaluation of potential preharvest interventions. The development of interventions strategies will require novel ideas, outside of the box thinking, and a willingness to step away from the attraction of putting a new spin on an old idea. Vaccines, bacteriophage, DFMs may yet produce the answer to *Salmonella* control pre-harvest, but the lack of results considering the efforts expended on these to date, suggest alternatives may win the day.

AUTHOR CONTRIBUTIONS

TE and TB conceived of the manuscript, and both contributed equally. All authors contributed to the article and approved the submitted version.

REFERENCES

Arsenault, R. J., Brown, T. R., Edrington, T. S., and Nisbet, D. J. (2022). Kinome Analysis of Cattle Peripheral Lymph Nodes to Elucidate Differential Response to *Salmonella* Spp. *Microorganisms* 10, 120. doi: 10.3390/microorganisms 10010120

Arthur, T. M., Brichta-Harhay, D. M., Bosilevac, J. M., Guerini, M. N., Kalchayanand, N., Wells, J. E., et al. (2008). Prevalence and Characterization of *Salmonella* in Bovine Lymph Nodes Potentially Destined for Use in Ground Beef. *J. Food Prot.* 71, 1685–1688. doi: 10.4315/0362-028X-71.8.1685

Cernicchiaro, N., Ives, S. E., Edrington, T. S., Nagaraja, T. G., and Renter, D. G. (2016). Efficacy of a *Salmonella* Siderophore Receptor Protein Vaccine on Fecal Shedding and Lymph Node Carriage of *Salmonella* in Commercial Feedlot Cattle. *Food. Path. Dis.* 13, 517–525. doi: 10.1089/fpd.2016.2129

Chlebicz, A., and Slizewska, K. (2018). Campylobacteriosis, Salmonellosis, Yersiniosis and Listeriosis as Zoonaotic Foodborne Diseases: A Review. *Int. J. Res. Public Health* 15, 863. doi: 10.3390/ijerph15050863

Edrington, T. S., Arthur, T. M., Loneragan, G. H., Genovese, K. J., Hanson, D. L., Anderson, R. C., et al. (2020). Evaluation of Two Commercially-Available *Salmonella* Vaccines on *Salmonella* in the Peripheral Lymph Nodes of Experimentally-Infected Cattle. *Ther. Adv. Vacc. Immuno.* 8, 1–7. doi: 10.1177/2515135520957760

Edrington, T. S., Callaway, T. R., Anderson, R. C., and Nisbet, D. J. (2008a). Prevalence of Multidrug-Resistant Salmonella on Commercial Dairies Utilizing a Single Heifer Raising Facility. *J. Food Prot.* 71, 27–34. doi: 10.4315/0362-028X-71.1.27

Edrington, T. S., Dowd, S. E., Farrow, R. F., Hagevoort, G. R., Callaway, T. R., Anderson, R. C., et al. (2012). Development of Colonic Microflora as Assessed by Pyrosequencing in Dairy Calves Fed Waste Milk. *J. Dairy Sci.* 95 (8), 4519–4525. doi: 10.3168/jds.2011-5119

Edrington, T. S., Hume, M. E., Looper, M. L., Schultz, C. L., Fitzgerald, A. C., Callaway, T. R., et al. (2004). Variation in the Faecal Shedding of *Salmonella* and *E. Coli* O157:H7 in Lactating Dairy Cattle and Examination of *Salmonella* Genotypes Using Pulsed-Field Gel Electrophoresis. *Lett. Appl. Microbiol.* 38 (5), 366–372. doi: 10.1111/j.1472-765x.2004.01495.x

Edrington, T. S., Loneragan, G. H., Genovese, K. J., Hanson, D. L., and Nisbet, D. J. (2016). *Salmonella* Persistence Within the Peripheral Lymph Node of Cattle Following Experimental Inoculation. *J. Food Prot.* 79 (6), 1032–1035. doi: 10.4315/0362-028X.JFP-15-325

Edrington, T. S., Loneragan, G. H., Hill, J., Genovese, K. J., Brichta-Harhay, D. M., Farrow, R. L., et al. (2013a). Development of Challenge Models to Evaluate the Efficacy of a Vaccine to Reduce Carriage of Salmonella in Peripheral Lymph Nodes of Cattle. *J. Food Prot.* 76, 1259–1263. doi: 10.4315/0362-028X.JFP-12-319

Edrington, T. S., Loneragan, G. H., Hill, J., Genovese, K. J., He, H., Callaway, T. R., et al. (2013b). Development of a Transdermal Salmonella Challenge Model in Calves. *J. Food Prot.* 76 (7), 1255–1258. doi: 10.4315/0362-028x.jfp-12-317

Edrington, T. S., Ross, T. T., Callaway, T. R., Martinez, C. H., Hume, M. E., Genovese, K. J., et al. (2008b). Investigation Into the Seasonal Salmonellosis in Lactating Dairy Cattle. *Epidemiol. Infect.* 136 (3), 381–390. doi: 10.1017/S0950268807008680

Fitzgerald, A. C., Edrington, T. S., Looper, M. L., Callaway, T. R., Genovese, K. J., Bischoff, K. M., et al. (2003). Antimicrobial Susceptibility and Factors Affecting the Shedding of *E. Coli* O157:H7 and *Salmonella* in Dairy Cattle. *Lett. Appl. Microbiol.* 37 (5), 392–398. doi: 10.1046/j.1472-765x.2003.01417.x

Hanson, D. L., Loneragan, G. H., Brown, T. R., Nisbet, D. J., Hume, M. E., and Edrington, T. S. (2015). Evidence Supporting Vertical Transmission of *Salmonella* in Dairy Cattle. *Epidemiol. Infect.* 144 (5), 962–967. doi: 10.1017/S0950268815002241

Healthy People (2020) *Healthy People 2020 Objectives and Topics: Food Safety* (healthypeople.gov: Office of Disease Prevention and Health Promotion) (Accessed February 02, 2021).

Heider, L. C., Meiring, R. W., Hoet, A. E., Gebreyes, W. A., Funk, J. A., and Wittum, T. E. (2008). Evaluation of Vaccination With a Commercial Subunit Vaccine on Shedding of *Salmonella Enterica* in Subclinically Infected Dairy Cows. *J. Am. Vet. Med. Assoc.* 233, 466–469. doi: 10.2460/javma.233.3.466

Hermesch, D. R., Thomson, D. U., Loneragan, G. H., Renter, D. R., and White, B. J. (2008). Effects of a Commercially Available Vaccine Against *Salmonella Enterica* Serotype Newport on Milk Production, Somatic Cell Count, and Shedding of *Salmonella* Organisms in Female Dairy Cattle With No Clinical Signs of Salmonellosis. *Am. J. Vet. Res.* 9, 1229–1234. doi: 10.2460/ajvr.69.9.1229

Koohmaraie, M., Arthur, T. M., Bosilevac, J. M., Guerini, M., Shackelford, S. D., and Wheeler, T. L. (2005). Post-Harvest Interventions to Reduce/Eliminate Pathogens in Beef. *Meat Sci.* 71, 79–91. doi: 10.1016/j.meatsci.2005.03.012

Li, M., Malladi, S., Hurd, H. S., Goldsmith, T. J., Brichta-Harhay, D. M., and Loneragan, G. H. (2015). *Salmonella* Spp. In Lymph Nodes of Fed and Cull Cattle: Relative Assessment of Risk to Ground Beef. *Food Control* 50, 423–434. doi: 10.1016/j.foodcont.2014.09.011

Loneragan, G. H., Thomson, D. U., McCarthy, R. M., Webb, H. E., Daniels, A. E., Edrington, T. S., et al. (2012). *Salmonella* Diversity and Burden in Cows on and Culled From Dairy Farms in the Texas High Plains. *Foodborne Path. Dis.* 9, 549–555. doi: 10.1089/fpd.2011.1069

Lyte, M., Frank, C. D., and Green, B. T. (1996). Production of an Autoinducer of Growth by Norepinephrine Cultured *Escherichia Coli* O157:H7. *FEMS Microbiol. Lett.* 139, 155–159. doi: 10.1111/j.1574-6968.1996.tb08196.x

McEntire, J., Acheson, D., Siemens, A., Eilert, S., and Robach, M. (2014). The Public Health Value of Reducing *Salmonella* in Raw Meat and Poultry. *J. Food Prot. Trends.* 34 (8), 386–392.

Nickelson, K. J., Taylor, T. M., Griffin, D. B., Savell, J. W., Gehring, K. B., and Arnold, A. N. (2019). Assessment of *Salmonella* Prevalence in Lymph Nodes of U.S. And Mexican Cattle Presented for Slaughter in Texas. *J. Food Prot.* 82, 310–315. doi: 10.4315/0362-028X.JFP-18-288

Olafson, P. U., Brown, T. R., Lohmeyer, K. H., Harvey, R. B., Nisbet, D. J., Loneragan, G. H., et al. (2016). Assessing Transmission of *Salmonella* to Bovine Peripheral Lymph Nodes Upon Horn Fly Feeding. *J. Food Prot.* 79, 1135–1142. doi: 10.4315/0362-028X.JFP-15-414

Redweik, G. A., Kogut, M. H., Arsenault, R. J., Lyte, M., and Mellata, M. (2021). Reserpine Improves Enterobacteriaceae Resistance in Chicken Intestine *via* Neuro-Immunometabolic Signaling and MEK1/2 Activation. *Comm. Biol.* 4:1359–1369. doi: 10.1038/s42003-021-02888-3

Sperandio, V., Torres, A. G., Jarvis, B., Naturo, J. P., and Kaper, J. B. (2003). Bacteria-Host Communication: The Language of Hormones. *Proc. Natl. Acad. Sci. U. S. A.* 100, 8951–8956. doi: 10.1073/pnas.1537100100

Webb, H. E., Brichta-Harhay, D. M., Brashears, M. M., Nightingale, K. K., Arthur, T. M., Bosilevac, J. M., et al. (2017). *Salmonella* in Peripheral Lymph Nodes of Healthy Cattle at Slaughter. *Front. Microbiol.* 8, 2214. doi: 10.3389/fmicb.2017.02214

Wheeler, T. L., Kalchayanand, N., and Bosilevac, J. M. (2014). Pre- and Post-Harvest Interventions to Reduce Pathogen Contamination in the U.S. Beef Industry. *Meat Sci.* 98 (3), 372–382. doi: 10.1016/j.meatsci.2014.06.026

Wottlin, L. R., Edrington, T. S., and Anderson, R. C. (2022). *Salmonella* Carriage in Peripheral Lymph Nodes and Feces of Cattle at Slaughter is Affected by Cattle Type, Region, and Season. *Front. Anim. Sci.* 3, 859800. doi: 10.3389/fanim.2022.859800

Conflict of Interest: TE was employed by Diamond V Mills. TB was employed by Cargill Inc.

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