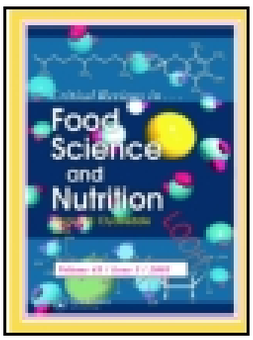

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Effects of antimicrobial use in agricultural animals on drug-resistant foodborne salmonellosis in humans: A systematic literature review

Kristi L. Helke[1], M.A. McCrackin[1,2], Ashley M. Galloway[3], Ann Z. Poole[3], Cassandra D. Salgado[4], Bernadette P. Marriott[5]

[1] Department of Comparative Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

[2] Ralph H. Johnson VA Medical Center Research Service, Charleston, South Carolina, USA

[3] Nutrition Section, Division of Gastroenterology, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

[4] Infectious Disease Division, Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA

[5] Nutrition Section, Division of Gastroenterology, Department of Medicine and Department of Psychiatry, Medical University of South Carolina, Charleston, South Carolina, USA

Address correspondence to:

Bernadette P. Marriott, Ph.D.

Professor and Director, Nutrition Section

Department of Medicine, Division of Gastroenterology and Hepatology

and Military Division, Department of Psychiatry and Behavioral Sciences

114 Doughty Street STB 630D, MSC 770

Charleston, SC 29425-7740

Email: marriobp@musc.edu

Last names listed as they should be indexed in PubMed: Helke; McCrackin; Galloway; Poole; Salgado; Marriott

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ABSTRACT

Controversy continues concerning antimicrobial use in food animals and its relationship to drug-resistant infections in humans. We systematically reviewed published literature for evidence of a relationship between antimicrobial use in agricultural animals and drug-resistant meat or dairy-borne non-typhoidal salmonellosis in humans. Based on publications from the United States (U.S.), Canada, and Denmark from January 2010 to July 2014, 858 articles received title and abstract review, 104 met study criteria for full article review with 68 retained for which data are presented. Antibiotic exposure in both cattle and humans found an increased likelihood of *Salmonella* colonization, whereas in chickens, animals not exposed to antibiotics (organic) were more likely to be *Salmonella* positive and those that had antibiotic exposure were more likely to harbor antimicrobial resistant *Salmonella* organisms. In swine literature, only tylosin exposure was examined and no correlation was found among exposure, *Salmonella* colonization, or antimicrobial resistance. No studies that identified farm antimicrobial use also traced antimicrobial-resistant *Salmonella* from farm to fork.

Keywords: food safety, tetracycline, streptomycin, farm-to-fork, meat

INTRODUCTION

Antibiotic resistance is a global threat that has received targeted national attention (CDC, 2013) and government action in the United States (U.S.) (PCAST, 2014). The Centers for Disease Control and Prevention (CDC) estimate that 2 million illnesses and 23,000 deaths annually are caused by antimicrobial-resistant bacteria and fungi domestically (CDC, 2013). All antimicrobial use creates selection pressure on microorganisms whether provided to humans, animals, or the environment (Doyle, *et al.*, 2006, 2012). Some human antibiotic-resistant infections are associated with foodborne illness (Friedman, 2015). Foodborne illness from both drug-sensitive and drug-resistant non-typhoidal *Salmonella* is estimated to sicken 1.2 million Americans annually (CDC, 2013; Scallan, *et al.*, 2011). Drug resistant non-typhoidal *Salmonella* is a pathogen of concern, with an estimated 100,000 annual domestic cases and 40 deaths from drug-resistant *Salmonella* (CDC, 2013). Between 1997 and 2011, *Salmonella* infections increased 17.1%, from 13.6 to 16.4 cases per 100,000 populace (U.S. Department of Health and Human Services, 2014). The U.S. Healthy People target for *Salmonella* for 2020 is 11.4 cases per 100,000 populace (U.S. Department of Health and Human Services, 2014).

Salmonellae are ubiquitous gram negative, motile, rod-shaped bacteria that can cause gastro-intestinal disease including diarrhea and fever in humans (de Jong, 2012). In animals, *Salmonella* can cause similar disease or be associated with an asymptomatic carrier state and protracted or periodic shedding. In addition to the clinical signs noted above, *Salmonella* infections may spread to the blood and have life-threatening complications (Crump, 2015).

The serovar, pathogenicity genes, and the dose of the organism all play a role in whether disease is caused in the host. Transmission to humans can occur from a variety of

sources including eggs, poultry, fish, meat, vegetables, contaminated water, and the handling of certain pets. Some *Salmonellae* can replicate within phagosomes which leads to increased pathogenicity (Brumell, *et al.*, 2002).

In order to understand the complexity of the issue of antimicrobial resistant (AMR) *Salmonellae*, it is important to understand the diversity of the pathogenic serovars. *Salmonella* species contain different variations of cell surface antigens, earning them designation as specific serotypes or serovars. Some serovars are only found in one kind of animal, in one specific environment and even in different parts of the world. Some serovars cause mild illness while others cause severe infection. *Salmonella* is quite different from other bacteria in that there are only two *Salmonella* species (*Salmonella bongori* and *Salmonella enterica*) and over 2,500 serotypes of *Salmonella enterica* alone (CDC, 2013). Of these, only a few are common pathogens in humans and animals. Some of the most common *Salmonella enterica* serovars include Agona, Cholerasuis, Derby, Enteritidis, Hadar, Heidelberg, Kentucky, Meleagridis, Newport, and Typhimurium, along with numerous others. Many serovars that colonize and infect humans other than Enteritidis and Typhimurium are not tracked (Wagenaar, *et al.*, 2013). Throughout this manuscript we will use '*Salmonella'* to mean non-typhoidal *Salmonella*.
Drug resistance in *Salmonella* is mediated by numerous mechanisms. *Salmonella* organisms may become resistant to antimicrobials by modifying or inactivating the antimicrobial agent, modifying the antimicrobial target, the action of the efflux pumps, or cell membrane permeability. All of these mechanisms may be mediated via mutations of the bacterial target protein, plasmids, integrons, or transposons (Walsh, 2000). Target proteins may be mutated via point mutations. Plasmids are self-replicating and can be transmitted to offspring, or between

two bacterial organisms. Transposons can self-excise and relocate any resistance genes they carry. Integrons carry one or more genes and may be integrated into chromosomal or plasmid DNA of the organism. A resistance gene present on a plasmid may be integrated into the bacterial chromosome if an integron is present (Mazel, 2006). There are numerous virulence genes, which are easily transmitted between bacteria of the same and different species, which leads to more difficult characterization of serovars, and results in differences in pathogenicity among serovars. Not only are virulence genes passed among bacteria, but drug resistance genes are passed as well, and as such, *Salmonella* may gain antimicrobial resistance from other organisms such as *E. coli* (Hamada, *et al.*, 2003).

There is widespread concern that first-line and sometimes second-line antibiotic therapy used to treat foodborne *Salmonella* have become ineffective; many serovars have developed multi-drug resistance (MDR) patterns. Resistant infections often require prolonged and more costly treatments, extended hospital stays, additional doctor visits and result in greater disability and death compared to infections that are more easily treatable with antibiotics (Broughton, *et al.*, 2010; Helms, *et al.*, 2004; Helms, *et al.*, 2002; Varma, *et al.*, 2005). While many scientific articles discuss the prevalence of *Salmonella*, fewer include the relationship to antibiotic resistance. Specifically, this review addressed the question: "Is there evidence from the literature that antimicrobial use in food animals is directly or indirectly involved in the emergence and spread of foodborne antibiotic-resistant *Salmonella*?" This systematic literature review was conducted to determine what is and is not known about the relationship between food animal production practices and the emergence and spread of antibiotic resistance, with emphasis on drug-resistant non-typhoidal *Salmonella*.

METHODS

Research Question and Approach

The review included all published research studies conducted in North America [the U.S. and Canada] and Denmark within databases searched; Denmark was included due to its long standing practice of restricting use of antibiotics in food animal production. The search time frame ended July 31, 2014. Search parameters were defined as: English, antibiotic resistance, *Salmonella* and food animal production. The project was narrowly focused on domestically acquired, foodborne illnesses associated with products from agricultural animals, so travel-associated diarrhea, direct animal contact, pet, plant and environmental contributors to human salmonellosis reports were excluded **(Table 1).** We have not screened the journals where the articles were published to determine if they are peer reviewed or not. The literature review process consisted of three phases: Phase 1: Title and Abstract Review; Phase 2: Full Article Review; and Phase 3: Final Library Creation (**Figure 1**).

An evidence-based approach was employed for collecting, reviewing and synthesizing the literature that was modeled after the processes used by the Agency for Health Care Research and Quality Evidence-based Practice Centers (EPC) (AHRQ, 2014). As such, a stepwise, systematic approach was used for literature inclusion, exclusion, data management, and evidence table presentation. The standard EPC approach was tailored for the task by including a mix of multidisciplinary, highly experienced scientific professionals (the team) who were knowledgeable in the specific areas of the review and by employing those elements pertinent to animal-based research from the evidence grading approach recommended by the Grades of

Recommendation, Development and Evaluation (GRADE) Working Group (Guyatt, *et al.*, 2011)(**Table 1**). It is important to note that while we could not employ the complete GRADE scoring approach, we did find that the GRADE system concept was applicable to these animal-based studies. This structured review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance **(Supplemental Table 1**) (Liberati, *et al.*, 2009;Moher, *et al.* 2009).

The team defined search parameters, inclusion and exclusion criteria and engaged in a bias discussion at the beginning of the project. All team members voiced that they could review and evaluate the literature on this topic fairly, disclosed no conflicts of interest, and signed a statement to this effect. No team members expressed opposition to the use of animals for food.

Search and Review Process

The SCOPUS[1] database (http://www.elsevier.com/online-tools/scopus), which incorporates PubMed citations and includes international publications, was selected for this review. A preliminary search was conducted to identify the depth and breadth of information available that limited the search parameters to English language, publication years 2005-2014, and document types: journal article, review, conference paper, article in press, or conference review. Based on the number of relevant articles identified in the preliminary review, the final document types were limited to published articles and articles in press from January 2010 through July 2014, review articles and position statements were excluded, and searches in the AGRICOLA database were added to identify more agricultural studies. A secondary search was conducted in the SCOPUS and AGRICOLA databases using the search string "human AND

[1] SCOPUS©, Elsevier, B.V., http://www.elsevier.com/online-tools/scopus

health AND agricultur* AND resistan*" to identify any pertinent publications on antibiotic resistance not specific to *Salmonella*. These final terms were determined after a more complete initial search had been completed on *Campylobacter* in a similar project (McCrackin, *et al.*, 2015).The final search terms are shown in **Table 2**.

For the title/abstract screening step of the review, the predetermined exclusion criteria were if the research article focus was: 1) not on antibiotic resistance, 2) on domesticated pets or their environment, 3) on plants and not on agriculture, 4) on experimental treatment of animals only, 5) not based in the U.S., Canada or Denmark, 6) a review article rather than primary literature or there was no abstract present, or 7) other. If the "other" category was selected, the reviewer was required to specify the reason for rejection.

For all citations for which full article review was conducted, information was systematically documented on the type of article (case study, observational/longitudinal, prevalence/incidence of disease, basic science, government report, other); animal species focus (n/a, beef, dairy, swine, poultry-all, fish/seafood, wild game, human, other); food processing (n/a, abattoir, processing/packaging, preparation); product (n/a, meat, milk, cheese, yogurt, other dairy, eggs, other) and antibiotic use (not mentioned, no, human, animal, laboratory/treatment, control, prevention, growth, resistance measured, other). The reviewers also summarized the article by recording the study duration, sample type, sample size, methods, results, and conclusion. The reviewer gave each publication a grade, based on the criteria in **Table 1**, and provided specific comments related to the rationale for the grade. One team member conducted the searches and compiled the results, four performed title/abstract screening and two conducted full article reviews. To manage the literature, provide transparency of the review process, and

rapid access to the data, all literature search results and reviews were captured in custom forms created using EndNote® x7 reference manager software[2]. The EndNote® reviewer form for each article included the review elements for both title/abstract screening (inclusion; if exclusion, reasons) and full article review (study purpose, type of article, species focus, food processing, product, antibiotic use, study duration, study sample type and size, method summary, results, conclusion and grade).

Applying the GRADE System

Each article receiving full article review was graded on the basis of quality, directness and consistency based on the GRADE approach for grading quality of evidence developed by the GRADE Working Group (Guyatt, *et al.*, 2011). The GRADE approach has been adopted by the Cochrane Collaboration for evaluating quality of evidence reported in systematic reviews in human research. We could not identify a similar grading system that had been used for animal research; therefore, we adapted GRADE for this review. In our review, two scores were given for quality, one based on evidence of statistical analysis and one based on the probability of bias or study design limitations. The directness score reflected whether the methods and results presented were clear and straightforward. The consistency score reflected whether the results and conclusions presented appeared to be consistent with the methods. Combining the three scoring categories, each article could receive a maximum grade of (+) four and a minimum grade of (-) six (**Table 1**).

[2] EndNote® x7, Thomson Reuters, http://endnote.com/product-details/X7

Results

Search Results, Screening and Review

SCOUPUS and Agricola were searched for articles on the subject of antimicrobial resistance in *Salmonella* and the relationship to food animals and production for the period of January 2010-July 31, 2014. We limited the search to the U.S., Canada, and Denmark. This search resulted in 858 articles for title and abstract review. Of these, 104 met the criteria for full article review. During full article review, an additional 36 were omitted leaving 68 for full article analysis (**Fig. 1, Table 2**).

The search was designed to determine if antibiotic usage in production animals has been shown to affect the prevalence of antimicrobial resistance and presence in humans. We found no studies that examined and described movement of antimicrobial-resistant *Salmonella* throughout the food production path from farm to table. Several studies examined up to three points along the production line, which includes feed, farm, lairage (resting area during transit to abattoir), abattoir (slaughterhouse), carcass, market and finally human consumption.

Journal Article Characteristics

Of the *Salmonella* articles that were kept for full article review, 52 were from the U.S., 11 from Canada, five from Denmark, and one each from Scotland and Ireland (**Table 3**). The article from Scotland was kept as it was a key paper that analyzed serovars from both animals and humans at the time of an outbreak, which was not found in literature from other countries (Mather, *et al.*, 2013). The article from Ireland addressed the role that disinfectants play in antimicrobial resistance (Condell, *et al.*,2012). Four reports looked at more than one country.

Not all literature mentioned the geographical location of the study or the origin of the samples. Of the final 68 *Salmonella* articles, 39 received a quality score of three or four. Sixteen received a score of zero to two and thirteen a score of less than zero (-6 is the lowest achievable score).

Article Characteristics

Type of article

Articles were assigned to one or more of the following groups: prevalence or incidence of disease (33), observational or longitudinal (28), basic science (10), case studies (6) and other (4).

Species Focus

Single species *Salmonella* articles included dairy (11), swine (10), poultry (chicken and turkey) (11), beef (7), and human (7). Twenty articles focused on more than one species with up to five species covered in one article. Two articles did not have a species focus and were basic science manuscripts.

Food Processing and Product

Articles were categorized as to where in the processing chain the sample was obtained, and also as to which product was sampled. Ten articles tested products from the abattoir, one article tested samples from the processing and packaging step of production, and seven articles obtained samples from preparation areas. Fifty-two articles did not obtain samples from the food processing chain. Twenty articles had results from meat samples, one from milk samples, one from eggs, and one from unspecified food products.

Antibiotic Use

There were no studies that provided details about specific antibiotic usage on farms, identification of isolates from farm to retail packaging, and linkage to human disease. Articles

were identified that addressed one or two of these steps on the path from farm to fork as follows: six articles showed increased drug-resistance in organisms derived from animals of conventional compared to antibiotic-free operations (Alali, *et al.*, 2010; Habing, *et al.*, 2012; M'Ikanatha, *et al.*, 2010; Mazengia, *et al.*, 2014; Sapkota, *et al.*, 2014; Zhang, *et al.*, 2011), two articles showed similar antibiotic resistant isolates on the farm and in the abattoir (Louden, *et al.*, 2012; Sjölund-Karlsson, *et al.*, 2013), and one article demonstrated an increase in antibiotic resistance of *Salmonella* in the presence of antibiotics (Rao, *et al.*, 2010). Three reports covered outbreak incidents where a similar isolate was identified in human samples and retail products (Green, *et al.*, 2014; Hoffmann, *et al.*, 2014; Schneider, *et al.*, 2011). No studies were found that followed animal-associated drug-resistant isolates from farm to retail products.

Laboratory Methods

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing methods were variable among the references. This is in part due to the advances in testing methods over the years. The United States Department of Agriculture (USDA) animal arm of the National Antimicrobial Resistance Monitoring System (NARMS) used the Sensititre broth microdilution system as the standard for testing (USDA, 2014). Different researchers used different panels of antibiotics ranging from four to 18 (Bearson, *et al.*, 2014; St. Amand, *et al.*, 2013). Over the years different antibiotics were determined to be more or less important in the NARMS resistance panel. For instance sulfamethoxazole was replaced by sulfisoxazole in 2004 and azithromycin replaced amikacin in 2011 (USDA, 2014). Most authors followed standardized guidance for antibiotic resistance

break points, but guidance evolved over the years, and break points changed in some cases. The break point for ciprofloxacin was redefined in 2012 by Clinical and Laboratory Standards Institute (CLSI), leading to increases in interpretation of resistance (Hombach, *et al.*, 2012).

Definition of Multi-Drug Resistance

A standard definition for multidrug resistance (MDR) was not found within the *Salmonella* literature. The NARMS and some others used the literal definition of resistant to more than one drug as multidrug resistant, whereas others did not classify *Salmonella* isolates as multidrug resistant unless they were resistant to five or more antimicrobials (Cook, *et al.*, 2011; Han, *et al.*, 2013; Louden, *et al.*, 2012; Marrero-Ortiz, *et al.*, 2012). Most references defined resistance to 3 or more antimicrobials as MDR.

Articles reviewed were primarily composed of prevalence articles along with those assessing antimicrobial resistance gene expression. Forty-two of the final 68 studies focused on antibiotic resistance in isolates from either animals or meat. Only six reports focused on the same issues in human isolates. Resistance plasmids, genes, and integrons were analyzed in 16 of the studies. Some studies assessed what effect antimicrobials had on the organism and addressed issues such as differences in gene expression and cell invasion. Three studies examined the effect of biocides used to clean the environment on *Salmonella* and found no difference in susceptibility to antimicrobials after exposure to biocides (Beier, *et al.*, 2011; Condell, *et al.*, 2012; Gantzhorn, *et al.*, 2014).

Prevalence of *Salmonella*

Serovar Prevalence

The most common serovars identified in this literature review varied among species, and many serovars are found in multiple species. Of the articles kept for full article review (n=68), eight did not mention which specific *Salmonella* serovar was detected; instead, these studies measured total *Salmonella* load.

Cattle

Cattle, both dairy and feedlot animals, were prone to colonization with serovars Typhimurium, Kentucky, Montevideo, Anatum, Cerro and 4,5,12:i (Cook, *et al.*, 2011; Cummings, *et al.*, 2013; Cummings, *et al.*, 2010; Gragg, *et al.*, 2013; Loneragan, *et al.*, 2012; Marrero-Ortiz, *et al.*, 2012; Rao, *et al.*, 2010; Rodriguez-Rivera, *et al.*, 2014; Soyer, *et al.*, 2013) (**Table 3**). These serovars do not always result in disease within cattle, and asymptomatic animals may shed *Salmonella* organisms. Among the aforementioned serovars, *Salmonella enterica* serotype Cerro prevalence is an increasing cause of illness in cattle, primarily dairy, across the U.S. and has been found to also be a cause of human illness (Cummings, *et al.*, 2013; Cummings, *et al.*, 2010; Hoelzer, *et al.*, 2010; Loneragan, *et al.*, 2012; Rodriguez-Rivera, *et al.*, 2014; Tewari, *et al.*, 2012).

In one interesting study, animals were tested and then inoculated with specific *Salmonella* serovars in order to study transmission of resistance genes between serovars. However, the serovars recovered at the end of the study, surprisingly, were not ones with which animals had been inoculated, suggesting that there can be silent infections, intermittent shedding of organisms (Edrington, *et al.*, 2013) or rapid clearance. Therefore organisms the animal is exposed to and are carrying are not necessarily the same serovar of the organisms that are shed.

Poultry

In poultry, samples from the farm environment, fecal matter, carcass rinsates and retail products resulted in the most common *Salmonella enterica* serovars isolated being Hadar, Kentucky, Enteritidis, Heidelberg and Typhimurium (Aslam, *et al.*, 2012; Beier, *et al.*, 2011; Diarra, *et al.*, 2014; M'Ikanatha, *et al.*, 2010; Mainali, *et al.*, 2014; Mazengia, *et al.*, 2014; Melendez, *et al.*, 2010; Sapkota, *et al.*, 2014). No pattern was noted to indicate the increased likelihood of the presence of specific serovars dependent upon whether or not antimicrobials were administered to the animals.

Swine

Farms and abattoirs were most commonly surveyed with fecal (direct and environment) and tissue samples, respectively, used for isolation of *Salmonella* organisms. Abattoir samples also consisted of carcass swabs from pre-and post-cleaning. These studies show that different serotypes are present before and after cleaning of the carcass (Schmidt, *et al.*, 2012). This indicates that organisms present on carcasses post cleaning are either more resilient (harder to clear away) or are deposited during the cleaning process. In swine, Typhimurium, Derby, Typhymurium var.5, and Heidelberg were the most commonly isolated serovars **(Table 3)** (Arguello, *et al.*, 2013; Aslam, *et al.*, 2012; Clothier, *et al.*, 2010; Deckert, *et al.*, 2010; Gantzhorn, *et al.*, 2014; Schmidt, *et al.*, 2012). In a study that examined historical isolates only from ill pigs on farms, the most prevalent isolates were Cholerasuis var. Kunzendorf followed by Typhimurium var. 5- (Clothier, *et al.*, 2010). Many pigs carry *Salmonella* organisms although they may be subclinical colonizations. In pigs, serovars found in the abattoir are highly variable depending on the stage of processing.

Human

In papers focused on human *Salmonella* infections, samples were most commonly fecal, urine, and blood. Most studies that examined human salmonellosis obtained samples from banked isolates and were thus retrospective, not prospective, in nature. In human infections, serovars Typhimurium, Newport, Heidelberg, and Enteritidis were identified most commonly (Folster, *et al.*, 2011; Glenn, *et al.*, 2011; Koningstein, *et al.*, 2010; Medalla, *et al.*, 2013; Solghan, *et al.*, 2010; Soyer, *et al.*, 2013). A few studies analyzed both human and animal isolates. Some showed no antimicrobial resistance (AMR) in humans, only in animals (Stepan, *et al.*, 2011), while others showed the opposite (Mezal, *et al.*, 2014). The disparity in these findings suggest that while transmission of organisms between food animals and humans may occur, there is not a consistent link in AMR between agricultural animals and humans. Studies that examined only human isolates have shown that *Salmonella* foodborne illness is more likely to be antimicrobial resistant if the person has taken antibiotics within the previous year (Koningstein, *et al.*, 2010).

Continuity between Animal and Human Isolates

A key factor in understanding the issues related to AMR in foodborne illness is linking the disease-causing human isolates to agricultural animal isolates. Many (15) articles attempted to link animal serovars with isolates from human clinical cases. While there was similarity among the serovars on some level, the origin of the isolates typically was too far removed to prove causation (**Table 4**). Correlation of antimicrobial resistance in animal *Salmonella* isolates with human disease was demonstrated in these studies, but not causation. Of the 15 articles, only one made a convincing argument (M'Ikanatha, *et al.*, 2010). In this study, samples were taken

from retail chicken and compared with isolates recovered from humans. There was one isolate from poultry that exhibited a PFGE pattern indistinguishable from a human isolate, and both isolates carried the resistance gene *bla*$_{\text{CMY-2}}$ (M'Ikanatha, *et al.*, 2010). Most reports attempting to show causation analyzed samples from farm animals, often those with clinical disease, which may or may not have been treated with antibiotics and then compared them with retrospective human clinical isolates from the local health department (Adhikari, *et al.*, 2010b; Green, *et al.*, 2014; Hoelzer, *et al.*, 2010; Soyer, *et al.*, 2013; Stepan, *et al.*, 2011). However, a study of beta-lactam resistance genes in human, animal and meat isolates showed that different genes were present in humans versus the animal and meat samples, suggesting that there may be evolutionary differences in AMR organisms in human and animal populations (Sjölund-Karlsson, *et al.*, 2013). Soyer et al. described the resistance genes present in isolates from both cattle and humans and failed to show convincing similarities, but showed that the two species had very different resistance gene patterns in their respective *Salmonella* isolates (Soyer, *et al.*, 2013).

Antimicrobial Resistance

Resistance in *Salmonella* spp. isolates varied. On farms, *Salmonella* was isolated from 0.95% - 77% of all samples (Cummings, *et al.*, 2010; Hoelzer, *et al.*, 2010; Rao, *et al.*, 2010). These wide variances are due to many factors, among them different practices on the farm, different sampling techniques, and different isolation techniques. Of the isolates, resistance was variable ranging from 0-98% (Aslam, *et al.*, 2012; Zou, *et al.*, 2012). The most prevalent resistance phenotype of *Salmonella* isolates during this timeframe in the U.S., Canada and Denmark was to tetracycline followed by resistance to streptomycin, although there was some

resistance found to all antibiotics tested (16 routinely, 43 overall). Tetracycline resistance was often associated with the presence of *tetA*, *tetB*, *tetC*, *tetG* and *tetR* genes (Louden, *et al.*, 2012). Beta-lactams, including cephalosporins, are clinically important in humans, and several studies were performed to assess the presence of genes specifically associated with resistance to these antimicrobials. The beta-lactam resistance gene *bla*CMY was found in many isolates including all serovars (Folster, *et al.*, 2010; Folster, *et al.*, 2011; Louden, *et al.*, 2012). The IncA/C plasmid was also present in many isolates and conferred multidrug resistance (Glenn, *et al.*, 2011; Marrero-Ortiz, *et al.*, 2012).

An outbreak of *Salmonella* in dairy cattle was described and monitored in Michigan with the only sign being increased shedding of the organism. Recovered organisms were non-pathogenic, yet did diverge throughout the course of the outbreak and most isolates were multidrug resistant (Kaneene, *et al.*, 2010). This highlights the complexity of the study of *Salmonella* organisms; they are constantly mutating and evolving. Shedding of *Salmonella* was examined by several groups and was not found to correlate with feeding of antimicrobials in pigs (Farzan, *et al.*, 2010; Kim, *et al.*, 2014), feed type in cattle (Edrington, *et al.*, 2011), or weaning of calves (Edrington, *et al.*, 2010). In one study in cattle, feeding ionophores (a non-therapeutic class of antibiotic used in ruminants to increase feed efficiency) was associated with increased odds of being *Salmonella* positive (Habing, *et al.*, 2012). Shedding was increased in animals with greater housing density (Farzan, *et al.*, 2010). This is suspected to be due to the added stress of housing many animals together with decreased individual space.

Discussion

It was rare to find reports that mentioned use of antimicrobials on the farm, and none of the studies included in our project had information on use of antimicrobials in an agricultural setting linked with antibiotic resistance in human isolates. There was not continuity between isolates from animals and humans, and there were even serovar differences found dependent upon anatomical location of where samples were collected from the same animal (e.g. feces, skin, intestinal contents). In all published reports, where *Salmonella* isolates were procured from the same animal species in different stages of production (e.g. on farm, abattoir, retail package), different serovar prevalence was identified. Not only does the site of sampling in or on the animal or animal product matter for isolation of organisms, but *Salmonella* is also found in vegetables and non-farm environmental samples.

Antibiotic Resistance Associated with Antibiotic Use in Food Animals

Very few reports examined antimicrobial resistance in *Salmonella* spp. and related it to the use of antimicrobials in food animals. A number of reports, which included poultry, beef, and pork, compared conventional to organic or antibiotic free husbandry systems. These articles have conflicting results with regard to number of isolates from samples, but all concluded that there were fewer antimicrobial resistant organisms found on animals and retail products raised in the absence of antimicrobials (Alali, *et al.*, 2010; M'Ikanatha, *et al.*, 2010; Mazengia, *et al.*, 2014; Sapkota, *et al.*, 2014).

Raising animals without antibiotics does not preclude the presence of resistance genes in *Salmonella* sp. isolates. *Salmonella* sp. with resistance phenotypes have been found in the

antibiotic-free feed of both pigs and chickens suggesting that resistance may not be associated with antimicrobial feed additives but to core feed components (Alali, *et al.*, 2010; Molla, *et al.*, 2010).

During an outbreak in Scotland, *Salmonella* DT104 isolates from humans with disease and animals, primarily cattle with or without disease, were collected and whole genome sequences were compared. The data indicated that separate clades were circulating in ill humans versus animals, yet even in this study there was not a complete data set from farm to table (Mather, *et al.*, 2013). Other reports support these findings and suggest serotypes diverge both by geographic region and by species (Hoelzer, *et al.*, 2010). These data suggest that antimicrobial resistance in *Salmonella* is complex and multifactorial.

The most recent NARMS report, which integrated both animal and human data, reveals that serovars present in retail meat samples are not consistent with serovars found in the cecal contents of animals or with what is found on abattoir samples (FDA, 2015). Only 50% of serovars found in human infection match serovars found in retail meat and poultry samples (FDA, 2015), suggesting that as many cases of human salmonellosis are associated with non-meat as meat products. These studies also highlight that there is still much we do not know about *in vivo Salmonella* infections and interactions of the organism within hosts.

Not only are *Salmonella* infections obtained from ingestion of meat and animal products, but many are also acquired by eating vegetables (IFSAC, 2015). While beyond the scope of this review, it is important to note that *Salmonella* are intracellular bacteria and are present within the cells of plants making washing foodstuffs ineffective at removing the bacteria (Schikora, *et al.*, 2012). Many additional environmental and wildlife sources of *Salmonella* exist that can serve as

reservoirs for human illness. In the discussion of national sources of foodborne illness, these potential reservoirs of bacterial contamination should not be overlooked and need additional research. Also of concern is the role that international travel plays in the spread and emergence of resistant bacteria. A recent study showed that most *Salmonella* serotype Enteritidis infections in humans that were resistant to quinolones were obtained abroad (O'Donnell, *et al.*, 2014).

There is no study in recent literature that convincingly shows that antimicrobial use in animals contributes to antibiotic resistance in *Salmonella sp.* In one study, *Salmonella* isolates from carcasses collected at various stages of processing at a pork plant displayed varying prevalence; serovars present at initial sampling were not always present at final sample point. The percent of *Salmonella* sp. positive isolates decreased from 91.2% positive to 3.7% positive on the chilled final carcass (Schmidt, *et al.*, 2012). This suggests that carcass contamination in early steps of meat processing may have low predictive value for *Salmonella* isolates found in retail products; however, these types of longitudinal studies were not present for our analysis.

Limitations

While this review was limited to only the most recent literature, published in English, from Canada, the U.S. and Denmark, we found specific limitations within the studies reviewed. A limitation of the *Salmonella* literature in general was that the studies rarely mentioned whether or not antibiotics were used in the feed, or if this point was mentioned, rarely were the antibiotics in the feed identified. Future studies will be greatly enhanced if they include information on the use of antibiotics on the farm, farm isolates, abattoir isolates, packing isolates and retail isolates. Many studies addressed two or three of these points, but there was no study linking all aspects for a cohesive conclusion. Another limitation is the geographic seclusion of most of the studies.

Some were completed in small areas of a state or only in one state. There were no nationwide *Salmonella* surveillance studies found in the literature over the time course of this report. We were able to employ a subset of the GRADE criteria, which were developed and are used for assessment of human clinical trials. We used the GRADE system because to our knowledge there is no similar literature scoring system for animal-based studies, which is a limitation for drawing conclusions from published animal research in general. However, we encourage others to at least employ this modified GRADE approach.

New Promising Methodology

The testing methods for identifying *Salmonella* are also evolving leading to more precise diagnoses and identification of isolates. Identification and genetic relatedness of *Salmonella* isolates are currently achieved using pulsed field gel electrophoresis (PFGE), which is considered the gold standard. There are two enzymes (*Xba*I and *Bln*I) commonly used to compare similar isolates. However, several research groups have shown that different serovars can have identical PGFE patterns, using both enzymes (Hoffmann, *et al.*, 2014; Rodriguez-Rivera, *et al.*, 2014). Studies were done using PFGE showing that isolates were identical using 2 enzymes, but when multi-locus variable number tandem repeat analysis (MLVA) methods were applied the isolates were not identical (Adhikari, *et al.*, 2010b; Litrup, *et al.*, 2010; Prendergast, *et al.*, 2011). Single nucleotide polymorphism (SNP) analysis can be used to distinguish *Salmonella* isolates from each other with greater confidence compared to PFGE (Hoffmann, *et al.*, 2014; Rodriguez-Rivera, *et al.*, 2014). Another technique being used to distinguish isolates is MLVA (Mezal, *et al.*, 2014). Most of the studies reviewed in this report used PFGE, but more

confidence in the data would be gained by using the more discriminating MLVA technique, which is specific for a longer DNA sequence, and not dependent on enzyme specific recognition and cut sites which are typically only 6 base pairs long. These advances in technology highlight some of the possible deficiencies in earlier conclusions.

Conclusions

Emphasis on antibiotic stewardship programs and training in veterinary and medical colleges, pharmacy schools, hospital administration programs, public health curricula, and public education, including agricultural education, is critical. Young et al. showed in a survey project with Canadian broiler chicken producers that participants in all aspects of the food to fork chain would benefit from education about foodborne illness and how to minimize its transmission (Young, *et al.*, 2010). We support the recent proposal by the President's Council of Advisors on Science and Technology to expand antibiotic stewardship programs broadly and to facilitate collection of prescribing and usage data that is needed for making evidence-based decisions in the future, both in human and veterinary medicine (PCAST, 2014). The long-term nature of tetracycline resistance in *Salmonella* underscores that sound decisions about antibiotic use need to be made before new classes of antibiotics are used in animals or humans, since we cannot predict in advance which bacteria may become stronger and which weaker from adaptations they make to survive antibiotic selection pressure.

Finally, it was most apparent that there is great need for a more robust data collection system and heightened publication expectations in the U.S. for transparency in antibiotic usage in both animals and humans. Only in this way will scientists ever sort through the puzzles of

which factors contribute to the persistence of antibiotic resistance and to what degree. There is great need to start with studies that follow *Salmonella* along the entire pathway from farm to fork to human illness.

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Table 1. Scoring system for generating a grade for articles that were kept for full article review based on the GRADE system [1]

Category	Scoring range
Quality	
Evidence of statistical analysis	0 = no evidence
	+2 = evidence
Probability of bias or design limitations	0 = none
	-1 = some
	-2 = high
Directness	-2 = not direct
Methods and Results presented were clear and straightforward	-1 = some uncertainty
	+1 = direct
Consistency - results and conclusions presented appeared to be consistent with methods	-2 = important inconsistency
	-1 = some inconsistency
	+1 = consistent

[1] Guyatt, G. H., et al,(2011)

Table 2. Final Search strings used for the *Salmonella* search with number of resulting citations, 2005-July 2014

Search String^	**Number of Articles Retrieved per Li**brary
SCOPUS SEARCH	
Salmonella AND resistan* OR antimicrobial AND food OR meat OR seafood OR egg OR milk OR cheese OR dairy OR poultry OR agri*	912 (2 duplicates) **910** added to library
Salmonella AND resistan* OR antimicrobial AND human AND animal OR agri*	434 (279 duplicates) **155** additional to library
TOTAL	**1065 citations**
AGRICOLA SEARCH	
Salmonella AND resistan? OR antimicrobial AND food OR meat OR seafood OR egg OR milk OR cheese OR dairy OR poultry OR agri?	**969**
Salmonella AND resistan? OR antimicrobial AND human AND animal OR agri?	90 (75 duplicates) **15** additional to library
TOTAL	**984 citations**

^Bolded terms appear in abstract

Table 3. Summary of studies investigating antimicrobial resistant *Salmonella serotypes* by animal species

Reference	Location	GRADE	*Salmonella serotypes*	Sample size/type	Location of sample	Organic vs. Conventional	Timeframe	Antimicrobial use*
Cattle (Beef/Dairy)								
Edrington, *et al.*, (2011)	Southwest US	4	not determined	Winter: 69 cows (group 1), 75 cows (group 2); Summer: 79 cows (group 1), 76 cows (group 2)/fecal	Farm (Dairy) 1 farm (>3000 head)	conventional	Twice in Jan 09, twice in Jul 09	3e
Gragg, *et al.*, (2013)	US (NV, CA, AZ, NM, TX, ND, SD, NE, MN, WI)	4	24 serotypes including: Reading, Newport, Typhimurium, Montevideo, Anatum	3327 subiliac lymph nodes	Abattoir 8 processing plants (4 feedlot cattle, 4 dairy cull cows)	n/a	Sep-Nov 2010, Feb-Mar 2011, Jul-Sep 2011	3e
Habing, *et al.*, (2012)	US (ID, NM, WA, TX, IN, IA, KY, MI,	4	not specified	Fecal and pen composite manure samples	Farm (Dairy) 265 farms in 17 states.	conventional	Jan-Aug 07	2d, 3e

	MN, MO, NY, PA, VT, WI)							
Loneragan, *et al.*, (2012)	US (TX)	4	Anatum, Kentucky, Cerro Montevideo, Muenster, Infantis, Muenchen, Newport, Meleagridis, Newington, Mbandaka Idikan, Agona, Kedougou, Typhimurium	706 paired fecal and hide swipe samples, 70 similar samples from healthy cows	Auction Culled dairy cows pre-sale from 9 farms	not specified	21days; Jun-Sep	3e
Rao, *et al.*, (2010)	Canada (Alberta)	4	Rubislaw, Saintpaul, Enteritidis, Mbandaka, 4,5,12:i:- and Typhimurium	25 fresh manure samples from 84 pens; newly arrived vs. pre slaughter	21 feedlots (with >5000 capacity)	convention al	Mar-Dec 04, one visit in spring, one in fall	2a,c, 3e
Rodriguez-Rivera, *et al.*, (2014)	US (NY)	4	Cerro, Kentucky, Typhimurium	8948 samples from environment	Farm (Dairy) 46 farms	not specified	Oct 07-Aug 09	3e

			including variant O5-, Newport, Anatum including variant 15+	(n=1420) and fecal from cow (n=7528); environmental consisted of calf housing, cow housing, sick pen, manure storage				
Cummings, Warnick, Elton, Gröhn, *et al.*, (2010)	US (NY)	4	Cerro, Kentucky, Montevideo, Newport, Typhimurium, Thompson	50-70 non-clinical dairy cows sampled per visit based on size of lactating herd, and any clinical cases suspected to be *Salmonella* (+), and environmental samples; 3 sampling periods at 4-8 week	Farm (Dairy) 57 herds	not specified	12 months	3e

				intervals				
Brunelle, *et al.*, (2013)	US	3	Typhimurium DT104, DT193	40 cattle isolates (type not specified); NADC library	NADC Library	N/A	unknown timeframe	3e
Cummings, *et al.*, (2013)	US	3	Typhimurium, Newport, Agona, Kentucky, 4,5,12:i:-, Cerro	Sick cattle, 2745 fecal, GI, organ isolates	Farm (Dairy) Clinical samples from Cornell University Animal Health Diagnostic Center	not specified	Jan1 2004, Dec31 2011	3e
Lanzas, *et al.*, (2010)	US (NY)	3	Typhimurium	715 fecal, blood and outbreak samples (sick animals), environmenta	Farm (Dairy) 1 farm	not specified	Nov2 2005 - Jan23 2006	3e

				l samples				
Kaneene, *et al.*, (2010)	US (MI)	3	Oranienburg	190 salmonella isolates from fecal and calf/maternity pen swabs (environmental)	Farm (Dairy) 8 herds, pre-weaned calves	conventional	Oct 2003 – Mar 2005	3e
Cummings, Warnick, Elton, Rodriguez-Rivera, *et al.*, (2010)	US (NY)	-1	Cerro	50-70 dairy cows sampled per visit based on size of lactating herd, suspected *Salmonella* (+) cases, and environmental samples; 3 sampling periods at 4-8 week intervals	Farm (Dairy) 57 herds	not specified	12 months	3e

Edrington, *et al.*, (2010)	US (TX)	-1	not specified	237 direct fecal samples	Farm (Agricultural research)	not specified	Nov 2006 - May 2007	3e
Marrero-Ortiz, *et al.*, (2012)	US (WI)	-1	Kentucky, Newport, Thyphimurium, Cerro, Dublin, Montevideo, Agona, Anatum, Infantis, Livingstone, Mbdanka, Meleagris, Muenster, diarrizonae (subspecies)	45 isolates from fecal samples	Samples sent to lab from sick dairy cattle	unknown	Jan 2006 - Nov 2007	3e
Edrington, *et al.*, (2013)	US (TX)	-2	Minnesota, Give (retrieved)/ Newport, Reading (inoculated)	98 fecal swabs from 14 bull calves	Farm (Experimental)	not specified	7 days	3e
Cook, *et al.*, (2011)	Canada (southwest Ontario)	-4	Heidelberg, Copenhagen, Typhimurium DT 104, Typhimurium	528 fresh raw grain-fed veal samples (20 to 130 g per piece)	Retail (Veal)	unknown	Feb 2003 - May 2004	3e

			, Montevideo,					
Poultry								
Alali, *et al.*, (2010)	US (NC)	4	Serogroups B, C	3 Organic farms (300 samples), 4 conventional farms (400 samples) / feed, water, and floor (feces)	1 poultry company with organic and conventional flocks	Organic, Conventional	2 broiler flock cycles: 60 days organic; 55 days conventional	2c,d 3e
Diarra, *et al.*, (2014)	Canada (British Columbia)	3	Kentucky, Typhimurium (LIT2-1, F-LIT2-2, F-LIT2-3, and F-LIT2-4), Enteritidis, Hadar, Heidelberg, Brandenburg (SAB-LIT), Thompson	unknown total; 193 salmonella isolates recovered from fecal, cecal and litter samples	Farm 35 commercial broiler farms	not specified	2005-2008	2c,d 3e

Mainali, *et al.*, (2014)	Canada (Alberta)	3	Hadar, Heidelberg, Blockley, I:4,5,12:i:2, Kentucky, Infantis, Copenhagen, Typhimurium, Agona, Mbandaka, I:ROUGH-O:z10:enx	Matched cecal / crop samples 30 birds / flock; 272 isolates from feces, skin, crop. 850 *Salmonell*a isolates	Abbatoir 63 flocks	Not specified	Nov 2004 – Apr 2005	3e
M'Ikanatha, *et al.*, (2010)	US (Central PA)	3	Typhimurium, Kentucky, Enteritidis, Mbandaka, Heidelberg, Braenderup, untypeable strains	378 meat samples (183 from grocery stores, 195 from farmers markets; 226 open display, 152 pre-packaged)	Retail 10 grocery stores, 8 farmers markets	Conventional, Organic, Antibiotic free	Monthly, Feb2006 - Jan 2007	3e
Sapkota, *et al.*, (2014)	US (mid-Atlantic region)	3	Kentucky, Orion, Enteritidis, Gostrup, Infantis	2 poultry houses/farm poultry litter (n=60), water samples (n=40) and feed samples (n=20) /house	Farm 5 conventional 5 organic farms	conventional, organic	Mar – Jun 2008	2b,c,d (conventional) 3e

				(20 houses total)				
Zhang, *et al.*, (2011)	US (IN)	3	not specified	201 conventional, 201 no-antibiotic meat samples, 10 brands, various cuts	Retail Large retail food outlets	convention al, no-antibiotics	Sep 2009 - Aug 2010	3e
Melendez, *et al.*, (2010)	US (AR)	2	Kentucky, Enteritidis, Bareilly, Mbdanka, Montevideo, Newport	200 samples (164 farm (feed, water, insects), 36 retail, processing plant (carcass) 59 isolates	Farm, Retail, processing plant	pasture raised, no antibiotics	not specified	3e
St. Amand, *et al.*, (2013)	Canada (Alberta)	2	Heidelberg	951 Salmonella Heidelberg isolates from animal and environment (litter, organs, lab)	Lab (originating from animals and farm)	unknown	1996 - 2010	3e

Beier, *et al.*, (2011)	US (2 distinct locations)	1	Derby, Hadar, Montevideo, Senftenberg, Agona, Anatum, Brandenburg, Meleagridis, Reading, Typhimurium	2 plants, 1200 carcass rinse samples from pre- and post-immersion chiller sampling sites	Abattoir 2 commercial turkey processing facilities	not specified	2 days in 2002 and 1 day in 2004	3e
Mazengia, *et al.*, (2014)	US (Seattle, WA)	1	Heidelberg, Enteritidis, Kentucky, Hadar, Schwarzengrund, Agona, Senftenberg, Litchfield, Berta, Mbandaka, Typhimurium, and monophasic Typhimurium variants	1,322 samples: 1094 conventional, 259 conventional with no antimicrobials, 228 USDA organic: 362 skinless/boneless breasts, 103 split breasts, 293 thighs, 149 drumsticks, 101 wings, 97 ground chicken, 180 ground	Retail 20-30 samples weekly from 3-5 grocery stores	Organic, Conventional, no-antibiotics	April 2011 - April 2012	3e

				turkey, and 37 gizzards/combo				
Thakur, *et al.*, (2013)	US (NC)	-1	Typhimurium	900 samples fecal (n=400) and environment (n=500) from 10 houses (1 house/farm)	Farm 10 commercial farms (1 production company)	Conventional	October 2010 - March 2011	3e
Swine								
Arguello, *et al.*, (2013)	Denmark	4	Typhimurium, Derby, Infantis, Livingstone, 4,5,12:i:-	298 farms, 10 samples / farm (2890 total); feces, floor. 1656 abbatoir samples (ileocaecal lymph nodes, carcass swabs)	Breeding farm, Production farm, Abattoir	not specified	2006 - 2008	3e

Deckert, *et al.*, (2010)	Cananda (Alberta, Saskatchewan, Manitoba, Ontaria, Quebec)	4	Typhimurium var. Copenhagen, Derby, London, Typhimurium, Infantis, Bovismorbificans, Brandenburg, I:4i:-, California, Heidelberg, Mbandaka, Orion, I4[5],12:i:-, Others	346 (89 herds) (year 2006), 532 (115 herds) (2007) and 480 (96 herds) (2008) fecal samples	Farm (Finishers)	convention al	2006 - 2008 Herds visited 1-3x / year	2a,c, d 3e
Farzan, *et al.*, (2010)	Canada (Ontario)	4	Typhimurium var Copenhagen, Derby, Typhimurium , Agona, Havana, London, Infantis, Putten, Brandenburg, Senftenberg,	1197 floor and direct fecal samples (80 farms). 2 pigs / pen, 5 pens / barn, 1 barn / farm (800 samples); 1 pooled sample of 5 floor	Farm	Convention al, No antibiotics	Jan-Jul 2004	3e

			Ohio, I:6,7, I:28, I:4,12:i:-	locations (397 samples)				
Kim, *et al.*, (2014)	US (MN)	4	Infantis, Livingstone, Typhimurium, Manhattan	120 pigs, 5 samples each every 3 weeks. 600 samples. 15 pigs/pen, 4 pens, 2 farms.	Farm	Experimental	12 weeks	2f, 3e
Gantzhorn, *et al.*, (2014)	Denmark	4	Derby, Typhimurium, Brandenberg, Heidelberg, Infantis, Yoruba, Sandiego, Livingstone, 4,5,12:i:-	465 swab samples from pig slaughterhouses; 232 pre-, 233 post-cleaning	Abattoir	n/a	May 2011 - February 2012	3e
Wells, *et al.*, (2010)	US	3	not specified	1 g fecal samples from each: Trial 1: 192 weaned piglets, Trial 2: 256 weaned	Farm	Experimental	Trial 1: July–August, 2004; Trial 2: February–March,	2f, 3e

				piglets. 3 rectal swabs/ pig, 1 fecal sample / pig			2005	
Clothier, *et al.*, (2010)	US (IA)	1	Cholerasuis var. Kunsendorf, Typhimurium Var.5, Derby, Heidelberg, Typhimurium , Agona, Infantis, Brandenburg, Mbandaka, 4:12:i:. London, Senftenberg, Muenchen, Anatum, Other	293 (year 2003), 395 (2008), tissue samples and intestinal swabs from clinically ill pigs	Banked lab samples (tissues, intestinal contents)	Unknown	2003, 2008	3e
Molla, *et al.*, (2010)	US	1	Serogroups A, B, C, D, E	15,176 samples from feed, fecal and environment; 9 farms (4 barns / farm, 3 farms /	Farm	not specified	October 2007 - November 2009	3e

				production system, 3 production systems)				
Wells, *et al.*, (2013)	US (NE)	1	not specified	unknown sample size; fecal and blood samples, skin swabs	Farm	Experimental	12 weeks	2d,f, 3e
Schmidt, *et al.*, (2012)	US	0	41 serotypes including: Infantis, Agona, London, Munster, Typhimurium, Derby, Ohio, Heidelberg, Brandenburg	4560 carcass swab samples: 1520 pre-scald, 1520 pre-evisceration, 1520 chilled (2 large pork-producing pants)	Abbatoir	Unknown	Summer 2007, spring 2008	3e
Human								
Koningstein, *et al.*, (2010)	Denmark	4	Typhimurium, Enteritidis, Others	4675 Typhimurium isolates, 12151 Enteritidis isolates, 5776 other	Data from Statens serum institute and National registry for Enteric	n/a	1997 - 2005	

				serotype isolates, 214325 controls	Pathogens			
Folster, *et al.*, (2010)	US	4	Heidelberg (with decreased susceptibility to Ceftiofur / Ceftriaxone	54 clinical laboratory isolates collected from ill persons	Banked Isolates	n/a	1996 - 2006	3e
Krueger, *et al.*, (2014)	US	3	Typhimurium, Newport, Enteritidis, Heidelberg, Infantis, Stanley	875 patients; blood, feces	Lab samples	n/a	24 months	3e
Solghan, *et al.*, (2010)	US (NY)	2	Typhimurium, Enteritidis, Newport, Heidelberg, Tennessee, Dublin, Paratyphi B, Cholerasuis, Agona, Concord, Infantis, Saintpaul,	2189 isolates; blood, feces, urine, other (abscess, bone, gall blader, wound, etc.)	Banked FoodNet isolates	n/a	2003 - 2007	3e

			Others					
Medalla, *et al.*, (2013)	US (All States)	1	Typhimurium, Entertitidis, Newport, Heidelberg, Others	24,903 isolates; Human blood, stool, urine	Banked CDC NARMS isolates	n/a	1996 - 2009	3e
Zou, *et al.*, (2012)	US (NC)	0	Entertitidis	425 clinical isolates	banked isolates	n/a	June 2009 - Septembe r 2010	3e
Folster, *et al.*, (2011)	US (All States)	-3	Typhimurium, Newport, Heidelberg, Agona, Dublin, Typhimurium Var O:5-, Bredeney, Enteritidis, I 4,12:i:-, Ohio, and Saintpaul	2163 isolates from ill persons	Banked CDC NARMS isolates	n/a	2007	3e
Other								
Condell, *et al.*, (2012)	Ireland	4	Typhimurium, Senftenberg, Enteritidis, Gaminara,	189 Salmonella strains, 48 serotypes	Lab strains, Not specified	n/a	not specified	

			Hvittingfoss	from clinical sources, food, environment, and water ***looked at use of biocides in meat processing- no correlate with increased antibiotic resistance***				

Table 4. Summary of miscellaneous studies investigating antimicrobial resistant *Salmonella serotypes*

Reference	Country	GRADE	*Salmonella serotypes*	Sample size/type	Location of sample	Organic vs. Conventional	Timeframe	Antimicrobial use*	Species
Multiple Species									
Kilonzo-Nthenge, *et al.*, (2013)	US (TN)	4	Arizonae, Pullorum, Gallinarum, Choleraesuis	286 raw meat samples; chicken (n = 93), beef (n = 99), and turkey (n = 94). 25 Retail stores	Retail	not specified	not specified	3e	poultry, beef
Mather, *et al.*, (2013)	Scotland and abroad	4	Typhimurium DT104	262 isolates from humans (n=142) and animals (n=120)	Banked isolates	n/a	1990 - 2011	3e	human, cow, pig, horse, sheep, poultry
Hoffman, *et al.*, (2014)	US and Brazil	4	Heidelberg	42 isolates; animal (n =9), retail meat (n =27), and	Banked isolates	not specified	1982 - 2011	3e	human, ground turkey

				human clinical (n= 7)					, anima l
Sangal, *et al.*, (2010)	US, Germany, France and other countries	4	Newport, Enteritidis, Kentucky, Typhimuri um, Parathyphi B	N=381 from France (52 isolates), Germany (70), the United States (224), and other countries (35)	Banked isolates	n/a	1918 to 2005	3e	huma n, many anima l specie s
Le Hello, *et al.*, (2011)	US, England, Wales, Denmark, France, Nigeria	4	Kentucky ST198	120 human isolates, 76 non-human isolates (44 chicken, Nigeria)(1 3 seafood, 7 turkey meat, Morocco), (1 river water, 1dried herbs,	Banked isolates	n/a	1959-2008	3e	huma n, chicke n, seafoo d, turkey

				North Africa), (1 chicken, Ethiopia)					
Aslam, *et al.*, (2012)	Canada (Alberta)	3	26 total including: Heidelberg, Hadar, Kentucky, Typhimurium, Typhimurium var. Copenhagen, Anatum, Meleagridis, Reading, Give, Johannesburg, Heidelberg	564 fresh meat samples including chicken (n =206), turkey (n =91), ground beef (n = 134) and pork (n = 133);	retail	not specified	May 2007 - April 2008	3e	chicken, turkey, beef, pork
Louden, *et al.*,(2012)	US	3	Typhimurium	120 isolates from chickens (n=32), swine (n=29), turkey	Banked isolates from NARMS	not specified	n/a	3e	turkey, chicken, pig, cow

				(n=31) and cattle (n=28)					
Glenn, *et al.*, (2011)	US	3	Typhimurium and Typhimurium var.5 (Copenhagen)	one each from cattle, poultry, and swine with at least the ACSSuT-R phenotype were selected for each year	Banked isolates from NARMS (farm / slaughter) Selected ACSSuT-resistant isolates	n/a	1997 - 2007	3e	cattle, poultry, swine
Green, *et al.*, (2014)	US (MN, WI, OH, CO, others)	3	Hadar	Clinical salmonella isolates from 19 case patients, and product (ground turkey) sample isolates (unspecified number)	State and local health departments in 13 states	n/a	27 Dec 10-29 Mar 11	3e	Human, poultry

Mollenkopf, *et al.*, (2011)	US (OH, NC)	3	not specified	1000 meat samples. 5 grocery stores, 20 products/ store: 10 fresh beef, 10 fresh pork (7 beef steak, 3 ground beef, 6 pork chops, 4 pork ribs)	retail	not specified		3e	Beef, pork
Soyer, *et al.*, (2013)	US (NY, VT)	3	51 serotypes including: Typhimurium, Newport, Heidelberg, Montevideo, Hadar, Enteritidis, 4,5,12:i:2, Agona	336 isolates from human (178) and bovine (158). 64 NY farms, 8 VT farms.	Clinical salmonellosis cases (human), routine veterinary submission (cattle), banked isolates	not specified	January - December 2004	3e	Cattle, human

Argüello, *et al.*, (2014)	Denmark	2	4,[5],12:i:-	86 swine, 7 cattle, and 1 poultry; fecal samples (rectal feces and floor fecal samples), floor surface samples, lymph nodes, carcasses, and environment	Banked isolates from farm, slaughterhouse	not specified	not specified	3e	Cattle, pig, poultry
Schneider, *et al.*,)2011)	US (CA, AZ, ID, NV)	2	Newport (MDR only)	42 isolates from humans and unspecified number ground beef product samples	Banked samples from FSIS and public health dept.	unknown	October 2007	3e	Cattle, human

				from retail store, beef suppliers, and beef grinding establishments					
Stepan, *et al.*, (2011)	US	2	Senftenberg	98 isolates: human, (22), animal (71) and feed/goose down (5)	banked isolates (CDC, ND veterinary diagnostic lab, National vet services lab Ames, IA)	n/a	not specified		human, pig, cow, horse, turkey, quail
Hoelzer, *et al.*, (2010)	US (NY, NJ, WA, ID, VT, OR)	0	Newport (195), Typhimurium (190), and 4,5,12:I (40)	425 salmonella isolates (222 bovine isolates from animals without clinical signs, 203 human	Banked isolates	not specified	January 2004 - May 2005		Cattle, human

				isolates from individuals with clinical signs)					
Tewari, *et al.*, (2012)	US (PA)	0	Typhimurium, Newport, Cerro, Typhimurium var5-, Montevideo, Agona	60 isolates from human clinical cases (50), animal (10) feces and carcass from dead and ill dairy cattle	Banked isolates	n/a	2005-2010	3e	Cow, human
Dutil, *et al.*, (2010)	Canada (Ontario, Quebec, Saskatchewan, British Columbia)	-1	Heidelberg	Unspecified number; fresh meat samples, Hospital-based and private clinical laboratory isolated human samples	Retail (chicken), Banked isolates CIPARS (human)	not specified	2003 - 2008	3e	Human, chicken

Glenn, *et al.*, (2013)	US and Canada	-1	Newport, Hadar, Typhimurium, Heidelberg, Enteritidis, Saintpaul	56 isolates: slaughter (US 12/ Canada 9), retail (US 9/ Canada 9), human (US 9/Canada 8)	Banked Isolates	not specified	not specified	3e	human, pig, chicken, cow, turkey
Han, *et al.*, (2013)	US (AR, WV)	-1	Enteritidis	54 isolates; humans (28), retail chicken (9), broiler farms – feed and environment (9), and egg production facilities (8)	Farm, banked isolates	not specified	2004 - 2009	3e	human, chicken, egg
Sjölund-Karlsson, *et al.*, (2013)	US, Canada (BC, SAS, ONT, QUE, MAR)	-1	Typhimurium var O:5–, Dublin, Kentucky	5041 salmonella isolates: humans (US 2380), food	Retail, Abattoir, Banked isolates	Unknown	2008	3e	human, chicken, turkey, beef,

				animals – carcass rinsates, swabs (US 1326/ Canada 446) and retail meat – chicken breast, leg, wing, ground turkey, ground beef, pork chops (US 491/ Canada 399)					pork
Adhikari, *et al.*, (2010a)	US (Pacific Northwest)	-2	Typhimurium	130 isolates (n=112 bovine, n=18 human)	Banked Isolates	not specified	over 20 years	3e	Cattle, human
Mezal, *et al.*, (2014)	US (AR)	-4	Enteritidis	60 isolates: 28 isolates from poultry	Poultry houses and AR Department	not specified	2010	3e	Human, chicken

				houses and AR regional lab, 32 clinical isolates	of Health banked isolates				

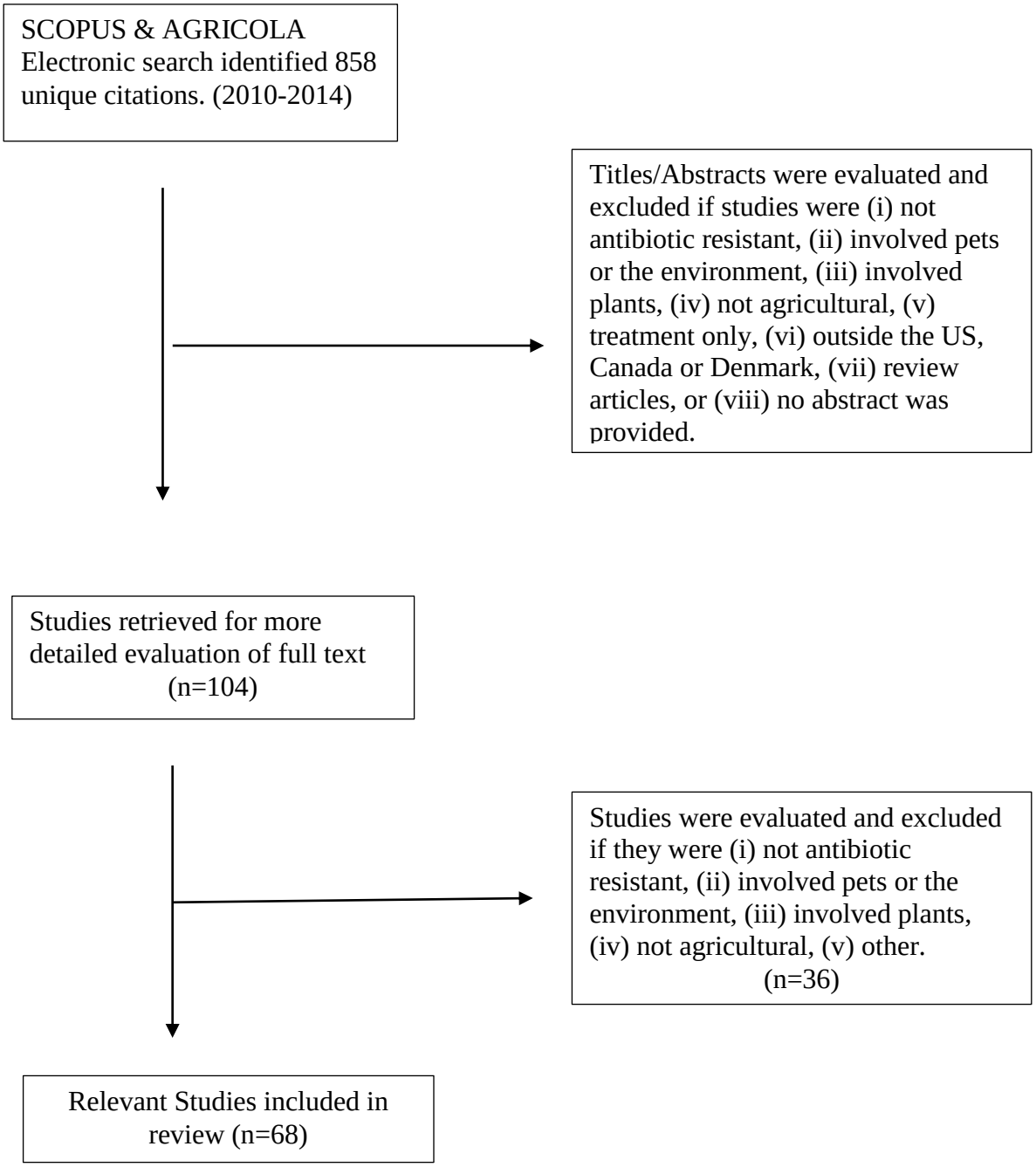

Figure 1. Workflow diagram adapted from Center for Reviews and Dissemination

