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Review article

The outbreaks and prevalence of antimicrobial resistant *Salmonella* in poultry in the United States: An overview

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HIGHLIGHTS

- The prevalence of antimicrobial resistance of *Salmonella* in the U.S. has been discussed.
- Usage of antimicrobial agents has increased in livestock.
- *Salmonella* has been developing resistance to antibiotics.
- Poultry linked *Salmonella* outbreaks are continuously increasing.
- Continuous monitoring of antimicrobial resistant *Salmonella* is crucial.

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ABSTRACT

Salmonella is a Gram-negative, rod-shaped, facultative anaerobic, and non-spore-forming bacterium that belongs to the family of Enterobacteriaceae and is the causative agent for typhoid/paratyphoid fever and salmonellosis. *Salmonella* causes the highest amount of foodborne illness among bacteria at 15.5 cases per 100,000 and causes an estimated 410,000 antibiotic-resistant infections each year in the U.S. The use of antibiotics has been a staple in poultry production for the prevention of diseases and growth promotion for the last 70 years. Due to the over-and misusage of antibiotics, there has been an emerging public health crisis. *Salmonella* is developing resistance and may render antibiotics inoperative in a foodborne outbreak. Poultry, when not handled properly, is a major carrier and transmitter of *Salmonella,* causing human illness and fatality. This review summarizes the major *Salmonella* outbreaks over the past three decades, the prevalence of Antimicrobial Resistant (AMR) *Salmonella* related to poultry, and the control measures being implemented to reduce and prevent AMR *Salmonella* in poultry.

1. Introduction

1.1. *Overuse of antimicrobial agents as an emerging public health crisis in the U.S.*

Antimicrobial agents including antibiotics have been used for the last 70 years in livestock and poultry agriculture to treat or prevent diseases and promote growth by increasing the rate of feed assimilation and lowering the incidence of mortality caused by an infectious agent (McEwen and Fedorka-Cray, 2002; Muaz et al., 2018; Yichao et al., 2019). Antimicrobials are often recognized as a group of agents that suppress the infection by killing or slowing the growth of pathogens including bacteria, parasites, viruses, and fungi. Antibiotics are drugs used to prevent and treat bacterial infections by killing particular bacteria (bactericidal) or preventing their multiplication (bacteriostatic) (CDC 2021d; WHO, 2022). The estimated total antimicrobial consumption related to livestock in 2010 was 63,151 $\pm$ 1,560 tons and it has been predicted that the antimicrobial consumption will rise 67% by 2030 (Boeckel et al., 2015). Pathogens such as *Salmonella* can be easily spread within a flock in poultry houses with higher stocking densities (Okwor and Eze, 2010; Shackleford, 1988). Antibiotics were intended only for diseased animals. However, due to the transfer of contamination from bird to bird, it is often more efficient to treat an entire flock by administering the antibiotics via the feed or water (McEwen and Fedorka-Cray, 2002).

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Various antibiotics have been invented since Sir Alexander Fleming discovered penicillin, the first commercialized antibiotic, in 1928 (CDC, 2020a). With the overuse of antibiotics, there is a growing concern that antibiotic resistant bacteria may carry over from farm animals to humans through various pathways. After a farm animal is treated with antimicrobials, the Antimicrobial Resistant (AMR) bacteria will exponentially multiply and out-compete non-resistant bacteria. During slaughter or processing, these resistant bacteria can contaminate food (Baker et al., 2018). AMR bacteria may be transmitted to humans through the consumption of adulterated food (Golkar et al., 2014). These bacteria may also enter the environment and spread to fruits, vegetables, and produce by the way of contaminated water. According to the Center for Disease Control and Prevention (CDC)'s Antibiotic Resistance Threats in the United States (U.S.) at least 2.8 million people annually become infected with AMR bacteria; resulting in more than 35,000 deaths in the U.S (CDC, 2019c). The first Antibiotic Resistance Threats Report was published by the CDC in 2013 and warned of the hazard of antibiotic resistance. From 2014 to 2019, it increased by an increment of 0.8 million infected people and nearly 12,000 deaths. Approximately 660,900 Americans were ill with infections caused by AMR foodborne bacteria each year (CDC, 2020d). *Salmonella* causes the highest amount of foodborne illness among bacteria at 15.5 cases per 100,000 and causes an estimated 410,000 antibiotic-resistant infections each year in the U.S (Wallinga et al., 2002). Antimicrobial resistance is estimated to rise if the usage of antimicrobial continues at the current rate, and as a result, 10 million people will be dying annually, resulting in a 2–3.5% reduction of Gross Domestic Product (GDP). It would cost the world nearly U.S. $100 trillion by 2050. It has been documented that 72.5% of medically important antibiotics are used in the U.S. for farm animals and 27.5% of antibiotics are used as treatments for humans (O'Neill, 2014).

1.2. *Salmonella* as a contamination source of poultry

Poultry products can be contaminated with various foodborne pathogens including *Salmonella*, *Campylobacter*, *Clostridium perfringens*, *Escherichia coli* 0157:H7, *Arcobacter,* and *Helicobacter* (Corry and Atabay, 2001; Mor-Mur and Yuste, 2009). A lot of evidence suggests that the contamination of poultry with *Salmonella* causes a serious public health issue, globally (Oosterom, 1991; Zhang-Barber et al., 1999). *Salmonella* is a gram-negative, rod-shaped, flagellated, and facultatively anaerobic bacterium. It belongs to the Enterobacteriaceae family, and characterized by O, H, and Vi antigens (Giannella 1996). Salmonellosis, an infection caused by *Salmonella*, is one of the most common and widely distributed foodborne diseases, with tens of millions of human cases occurring worldwide every year (WHO, 2020). In the U.S., there are more than 1.35 million salmonellosis cases each year causing more than 26,500 hospitalizations and 420 deaths (CDC, 2022). Estimated drug-resistant *Salmonella* infections caused by nontyphoidal *Salmonella* and *Salmonella* serotype Typhi are approximately 216,600 and the deaths related to drug-resistant *Salmonella* are nearly 75 per annum (CDC, 2020b). Non-typhoidal *Salmonella* has displayed a 3% resistance to both ciprofloxacin and ceftriaxone (predominate antibiotics used to treat *Salmonella* infections) and 5% resistance to five or more types of drugs (CDC, 2014b).

Non-typhoidal serovars of *Salmonella enterica* (NTS) are the most predominant zoonotic pathogens which affect humans as well as other animals (EFSA, 2018). Non-typhoidal *Salmonella* infections are caused by strains other than *S.* Typhi and *S.* Paratyphi A. Even though these strains are the most common bacterial pathogens causing gastrointestinal infections, the mortality rate is generally between 1–3.6%. Once ingested, non-typhoidal *Salmonella* has an incubation period from 4 to 12 h before symptoms are noticed (FDA, 2012; WHO, 2020). The symptoms may vary from mild to moderate gastroenteritis, consisting of diarrhea, abdominal cramps, vomiting, as well as, headaches, and fever (FDA, 2012; Foley, 2008; WHO, 2020). Depending on the level ingested, strain characteristics, and host factors, the symptoms may last from 4 to 7 days. Those at risk are infants, the elderly, and the immunocompromised who may become ill after ingesting as little as one cell. Healthy adults may become symptomatic after consuming 10^6–10^8 colony forming units. The complications usually associated with nontyphoidal salmonellosis are dehydration, electrolyte imbalance, and arthritis (FDA, 2012; WHO, 2020).

2. Intervention of the government regulatory agencies to fight against AMR

Government agencies have been leading the combat against AMR since 2013, after CDC released the report on Antibiotic Resistance Threats in the U.S. The report was able to gain the attention of the government and a five-year action plan, which is also known as the National Action Plan for Combating Antibiotic Resistant Bacteria (CARB), was declared to detect, prevent, and respond to AMR threats. As the leading country to fight AMR threats, the U.S. government agencies have been focusing on collaboration, innovation, and early adoption of aggressive action to achieve the goals of the action plan (CDC, 2019d).

The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) was established to provide advice, information, and recommendations to the Secretary of Health and Human Services regarding programs and policies intended to support and evaluate the implementation of U.S. government activities related to combating antibiotic-resistant bacteria. Initially, the PACCARB was established on September 18, 2014, under Executive Order 13676. Later, on March 3, 2020, the U.S. President delegated his authority to the Secretary of Health and Human Services under section 9(a) (1) of the Federal Advisory Committee Act (FACA), Public Law 92–463, as amended (5 U.S.C. App.), to re-establish the PACCARB (U.S. Department of Health & Human Services, 2022). The PACCARB pays attention and gives necessary recommendations on improving the effectiveness of antibiotics, developing innovative methods for reducing AMR (including new treatments, rapid diagnostics, alternatives to antibiotics, alternatives to animal antibiotics), surveillance of AMR bacterial infections, updating the health care providers and the public about AMR and methods to prevent, and reduce AMR and AMR bacterial infections (U.S. Department of Health & Human Services, 2020).

The National Antimicrobial Resistance Monitoring System (NARMS), a collaborative project amongst the CDC, U.S. Food and Drug Administration (FDA), and U.S. Department of Agriculture (USDA) (FDA, 2019a) was established in 1996. The objectives of NARMS are to: (1) Monitor trends in antimicrobial resistance in foodborne bacteria from humans, retail meats, and animals, (2) Adequately distribute data and information on antimicrobial resistance to enhance interventions that reduce resistance among foodborne bacteria, (3) Conduct research to understand the emergence, persistence, and spread of antimicrobial resistance, and (4) Assist the FDA in decisions related to the approval of safe and effective antimicrobial drugs for food-producing animals (FDA, 2018).

The CDC works closely with state and local governments to track antibiotic resistance and study patterns of emerging, resistant foodborne bacteria that are causing human illnesses. The CDC, through NARMS, tests bacteria transmitted through food outbreaks to determine their antibiotic susceptibility. The resistance patterns and mechanisms may assist investigators in identifying the source of an outbreak (FDA, 2019a).

3. *Salmonella* related outbreaks are linked to poultry products in the U.S.

This review summarizes the information on *Salmonella* related outbreaks during the past three decades and the antibiotic resistance related to those outbreaks. From 1990 to 2012, there were 45 *Salmonella* outbreaks linked to live poultry causing a total of 1,563 illnesses, 221 hospitalizations, and five deaths. All the reported *Salmonella* outbreaks in the past decade (2011–2021) were summarized in Table 1.

In 2011, there was a *Salmonella* Heidelberg outbreak linked to ground turkey infecting 136 people which included 37 being hospitalized and one death reported in a multi-state outbreak. The strains isolated from

Table 1. Reported *Salmonella* outbreaks linked to live poultry and poultry products.

Year	Related Product	*Salmonella* Strain	Antibiotic resistance was shown for at least one strain	Number of Cases	Number of Hospitalizations	Number of Deaths	Number of States	Reference
2021	Backyard Poultry	*Salmonella* Enteritidis *Salmonella* Hadar *Salmonella* Indiana *Salmonella* Infantis *Salmonella* Mbandaka *Salmonella* Muenchen	amoxicillin-clavulanic acid, ampicillin, chloramphenicol, cefoxitin, ceftriaxone*, ciprofloxacin*, gentamicin, kanamycin, streptomycin, sulfamethoxazole, tetracycline, trimethoprim-sulfamethoxazole	1135	273	2	48	CDC, 2021a
2021	Raw Frozen Breaded Stuffed Chicken Products	*Salmonella* Enteritidis	No resistance showed to tested antibiotics	36	12	0	11	CDC, 2021b
2021	Ground Turkey	*Salmonella* Hadar	Streptomycin, Tetracycline	33	4	0	14	CDC, 2021c
2020	Backyard Poultry	*Salmonella* Hadar *Salmonella* Braenderup *Salmonella* Muenchen *Salmonella* Thompson *Salmonella* Typhimurium *Salmonella* Newport *Salmonella* Agona *Salmonella* Anatum *Salmonella* Enteritidis *Salmonella* Infantis *Salmonella* Mbandaka *Salmonella* I4,[5],12:i:-	amoxicillin-clavulanic acid, ampicillin, cefoxitin, ceftriaxone*, chloramphenicol, fosfomycin, gentamicin, streptomycin, sulfisoxazole, tetracycline, trimethoprim-sulfamethoxazole.	1722	333	1	50	CDC, 2020c
2019	Backyard Poultry	*Salmonella* Agona *Salmonella* Alachua *Salmonella* Altona *Salmonella* Anatum *Salmonella* Braenderup *Salmonella* Enteritidis *Salmonella* Infantis *Salmonella* Manhattan *Salmonella* Montevideo *Salmonella* Muenchen *Salmonella* Newport *Salmonella* Oranienburg	amoxicillin-clavulanic acid, ampicillin, cefoxitin, ceftriaxone*, chloramphenicol, ciprofloxacin*, fosfomycin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, trimethoprim-sulfamethoxazole.	1134	219	2	49	CDC, 2019a
2019	Ground Turkey	*Salmonella* Schwarzengrund	ampicillin, gentamicin, streptomycin, sulfisoxazole, tetracycline.	7	1	0	3	CDC, 2019b
2018	Backyard Poultry	*Salmonella* Seftenberg *Salmonella* Montevideo *Salmonella* Infantis *Salmonella* Enteritidis *Salmonella* Indiana *Salmonella* Litchfield	ampicillin, streptomycin, sulfamethoxazole, tetracycline, gentamicin, ceftriaxone*, amoxicillin-clavulanic acid, cefoxitin, ciprofloxacin*, fosfomycin.	334	56	0	47	CDC, 2018a
2018	Shell Eggs	*Salmonella* Braenderup	No resistance showed to tested antibiotics	45	11	0	10	CDC, 2018b
2018	Raw Chicken Products	*Salmonella* Infantis	ciprofloxacin*, ceftriaxone*, ampicillin, chloramphenicol, fosfomycin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfisoxazole, trimethoprim-sulfamethoxazole, tetracycline.	129	25	1	32	CDC, 2018c CDC, 2018d
2018	Kosher chicken products	*Salmonella* I4,[5],12:i:-	No resistance showed to tested antibiotics	25	11	1	6	CDC, 2018e
2018	Raw Turkey Products	*Salmonella* Reading	ampicillin, streptomycin, sulfamethoxazole, gentamicin, tetracycline, fosfomycin, kanamycin, nalidixic acid, ciprofloxacin*, trimethoprim-sulfamethoxazole.	358	133	1	42	CDC, 2018f
2018	Chicken Salad	*Salmonella* Typhimurium	amoxicillin-clavulanic acid, ampicillin, cefoxitin, ceftriaxone*, gentamicin, streptomycin, sulfamethoxazole, tetracycline	265	94	1	8	CDC, 2018g
2017	Backyard Poultry	*Salmonella* Braenderup *Salmonella* Enteritidis *Salmonella* Hadar *Salmonella* I4,[5],12:i- *Salmonella* Indiana *Salmonella* Infantis	No information available	1120	249	1	48	CDC, 2017

(*continued on next page*)

Table 1 (*continued*)

Year	Related Product	*Salmonella* Strain	Antibiotic resistance was shown for at least one strain	Number of Cases	Number of Hospitalizations	Number of Deaths	Number of States	Reference
		Salmonella Litchfield *Salmonella* Mbandaka *Salmonella* Muenchen *Salmonella* Typhimurium						
2016	Backyard Poultry	*Salmonella* Enteritidis *Salmonella* Braenderup *Salmonella* Indiana *Salmonella* Hadar *Salmonella* Mbandaka *Salmonella* Infantis *Salmonella* Muenster	No information available	895	209	3	48	CDC, 2016e
2016	Shell Eggs	*Salmonella* Oranienburg	No information available	8	2	0	3	CDC, 2016f
2015	Backyard Poultry	*Salmonella* Enteritidis *Salmonella* Hadar *Salmonella* Indiana *Salmonella* Muenchen *Salmonella* Muenster	Sulfisoxazole	252	63	0	43	CDC, 2015a
2015	Raw, Frozen, Stuffed Chicken Entrees (Aspen Foods)	*Salmonella* Enteritidis	All isolates were susceptible to all antibiotics tested	5	2	0	1	CDC, 2015b
2015	Raw, Frozen, Stuffed Chicken Entrees (Barber Foods)	*Salmonella* Enteritidis	ampicillin tetracycline	15	4	0	7	CDC, 2015c
2014	Backyard Poultry	*Salmonella* Infantis *Salmonella* Newport	Tetracycline	363	120	0	43	CDC, 2014a
2014	Chicken	*Salmonella* Heidelberg	ceftriaxone*, combinations of the following antibiotics: ampicillin, cefoxitin, ceftiofur, amoxicillin/ clavulanic acid, sulfisoxazole, tetracycline, trimethoprim/ sulphamethoxazole.	9	2	0	1	CDC, 2014c
2013	Chicken	*Salmonella* Heidelberg	ampicillin, chloramphenicol, gentamicin, kanamycin, streptomycin, sulfisoxazole, tetracycline.	634	241	0	29	CDC, 2013d
2013	Backyard Poultry	*Salmonella* Typhimurium	No information available	356	62	0	39	CDC, 2013b
2013	Live Poultry	*Salmonella* Infantis *Salmonella* Lille *Salmonella* Newport *Salmonella* Mbandaka	No information available	158	29	0	30	CDC, 2013c
2013	Chicken	*Salmonella* Heidelberg	amoxicillin/clavulanic acid, ampicillin, ceftriaxone*	134	33	0	13	CDC, 2013e
2012	Backyard Poultry	*Salmonella* Hadar	No information available	46	13	0	11	CDC, 2012d
2012	Backyard Poultry	*Salmonella* Montevideo	No information available	93	21	1	23	CDC, 2012e
2012	Backyard Poultry	*Salmonella* Infantis, *Salmonella* Newport, *Salmonella* Lille	No information available	195	34	2	27	CDC, 2012f
2011	Kosher Broiled Chicken Livers	*Salmonella* Heidelberg	No information available	190	30	0	6	CDC, 2011b
2011	Ground Turkey	*Salmonella* Heidelberg	ampicillin, streptomycin, tetracycline, and gentamicin	136	37	1	34	CDC, 2011c
2011	Chicks Ducklings	*Salmonella* Altona *Salmonella* Johannesburg	No information available	68	19	0	20	CDC, 2011a
2011	Turkey Burgers	*Salmonella* Hadar	ampicillin, amoxicillin/ clavulanate, cephalothin, tetracycline.	12	3	0	10	CDC, 2011d

* The antibiotics used as the treatment agents for human *Salmonella* infections.

the ground turkey samples were resistant to ampicillin, streptomycin, tetracycline, and gentamicin. The human isolates were sensitive to common clinical practice antibiotics such as ciprofloxacin, ceftriaxone, and trimethoprim-sulfamethoxazole (Folster, 2012). Another *Salmonella* Heidelberg outbreak occurred in the same year leading to 190 infected people and 30 hospitalizations. The source of the outbreak was Kosher broiled chicken livers. Besides, *Salmonella* Altona and *Salmonella* Johannesburg outbreaks that occurred in multi states in the U.S. in 2011 resulted in 19 hospitalizations out of 68 infected people but no reported deaths. After epidemiological investigation, it has been revealed that the infection was linked to chicks and ducklings (CDC, 2011a). Also, the *Salmonella* Hadar outbreak occurred in 2011, and 12 people got sick and three patients were hospitalized. The strain was resistant to ampicillin, amoxicillin/clavulanate, cephalothin, and tetracycline (CDC, 2011d).

A large occurrence in 2012 was reported with eight *Salmonella* outbreaks (The Center for Disease Dynamics, Economics & Policy, 2013) including *Salmonella* Hadar (CDC, 2012a), *Salmonella* Montevideo (CDC, 2012b), *Salmonella* Infantis, *Salmonella* Newport, and *Salmonella* Lille (CDC, 2012c). The outbreaks were linked to live poultry in multiple states which resulted in the hospitalization of infected people and reported deaths.

In 2013, there were two *Salmonella* Heidelberg outbreaks linked to chicken. The largest outbreak reported 634 cases and 241 hospitalizations in 2013 caused by *Salmonella* Heidelberg, which was resistant to ampicillin, chloramphenicol, gentamicin, kanamycin, streptomycin, sulfisoxazole, and tetracycline. It has been reported that 31% of isolates were multidrug-resistant. The second *Salmonella* Heidelberg outbreak caused 134 illnesses of which 33 were hospitalized. Out of fourteen isolates recovered from this outbreak, 12 were susceptible to all tested antimicrobials and the other two were resistant to amoxicillin/clavulanic acid, ampicillin, and ceftriaxone. It has been reported that the resistant strains were mediated by the presence of an IncI1 plasmid carrying a $bla_{\text{CMY-2}}$ gene (CDC, 2013a). In the same year, two other outbreaks were reported after claiming 356 people infected by *Salmonella* Typhimurium in 39 states and 158 persons infected with *Salmonella* Infantis, *Salmonella* Lille, *Salmonella* Newport, or *Salmonella* Mbandaka in 30 states which were linked to poultry. The year 2013 appeared to have the highest number of *Salmonella* cases reported in the first half of the last decade and the highest number of hospitalizations reported in the entire decade linked to the poultry (Figure 1). However, there were no reported deaths (Figure 2) because, although outbreak strains were resistant to multiple drugs, those resistant drugs were not typically used to treat *Salmonella* bloodstream infections or other severe *Salmonella* infections (CDC, 2013d). Common first-line oral antibiotics for susceptible *Salmonella* infections are fluoroquinolones (for adults) and azithromycin (for children). Ceftriaxone is an alternative first-line treatment agent for *Salmonella* infections (CDC, 2018d).

Salmonella Heidelberg infected nine people in 2014 linked with mechanically separated chicken at a correctional facility and 2 of them were hospitalized. Two isolates (22%) exhibited multi-drug resistance to ceftriaxone. In addition, two isolates have shown resistance to combinations of the following additional antibiotics: ampicillin, cefoxitin, ceftiofur, amoxicillin/clavulanic acid, sulfisoxazole, tetracycline, and trimethoprim/sulphamethoxazole (CDC, 2014c). In 2014, CDC reported an outbreak linked to live poultry in backyard flocks which resulted in 363 infected people and 33% of them were hospitalized within 43 states due to strains of *Salmonella* Infantis, *Salmonella* Newport. Among them, two isolates were resistant to tetracycline (CDC, 2014a).

Raw, frozen, stuffed, and breaded chicken entrees distributed by two companies in 2015 recalled their product due to *Salmonella* outbreaks in 2015 as five people who consumed these products produced by Aspen Foods were infected with *Salmonella* Enteritidis in Minnesota. Two of these ill people were hospitalized, and no antibiotic resistance was reported (CDC, 2015b). In contrast, resistance to ampicillin and tetracycline was shown in the isolates recovered from raw, frozen, stuffed chicken entrees produced by Barber Foods which resulted in 15 infected people and four hospitalizations. These findings indicate that antibiotic resistance may be associated with increased risk of hospitalization, development of a bloodstream infection, or treatment failure in patients of seven states (CDC, 2015c). Furthermore, sulfisoxazole resistant isolates were reported in the investigation of four multistate outbreaks of human *Salmonella* infections linked to live poultry in backyard flocks caused by *Salmonella* Enteritidis, *Salmonella* Hadar, *Salmonella* Indiana, *Salmonella* Muenchen, and *Salmonella* Muenster in 2015. Two hundred fifty-two people infected and 63 ill people were hospitalized due to these four outbreaks among 43 states and no deaths were reported (CDC, 2015a).

Approximately 900 infected cases were reported within 48 states resulting in 209 hospitalizations and three deaths in 2016 due to human *Salmonella* outbreaks linked to live poultry in backyard flocks. Though the majority of the patients (249) were infected by *Salmonella* Enteritidis in 25 states, a total of 219 people were infected with *Salmonella* Infantis in 39 states. *Salmonella* Braenderup, *Salmonella* Indiana, *Salmonella* Hadar, *Salmonella* Mbandaka, *Salmonella* Infantis, and *Salmonella* Muenster infected 129, 110, 86, 46, 31, and 25 people, respectively (CDC, 2016e). Moreover, eight people were infected with *Salmonella* Oranienburg from a multistate (three) outbreak in 2016. According to investigations shell eggs were the source of contamination (CDC, 2016f).

In 2017, more than 1100 people infected with *Salmonella* in 10 separate multistate outbreaks spread over 48 states and the District of Columbia due to contact with backyard poultry flocks. The outbreaks resulted in 249 hospitalizations and one death. The strains of infection were: *Salmonella* Braenderup, *Salmonella* Enteritidis, *Salmonella* Hadar, *Salmonella* I4,[5],12:i-, *Salmonella* Indiana, *Salmonella* Infantis, *Salmonella* Litchfield, *Salmonella* Mbandaka, *Salmonella* Muenchen, and *Salmonella* Typhimurium (CDC, 2017).

In 2018, multiple states reported multidrug-resistant *Salmonella* Reading infections linked to raw turkey products which ended up occurring

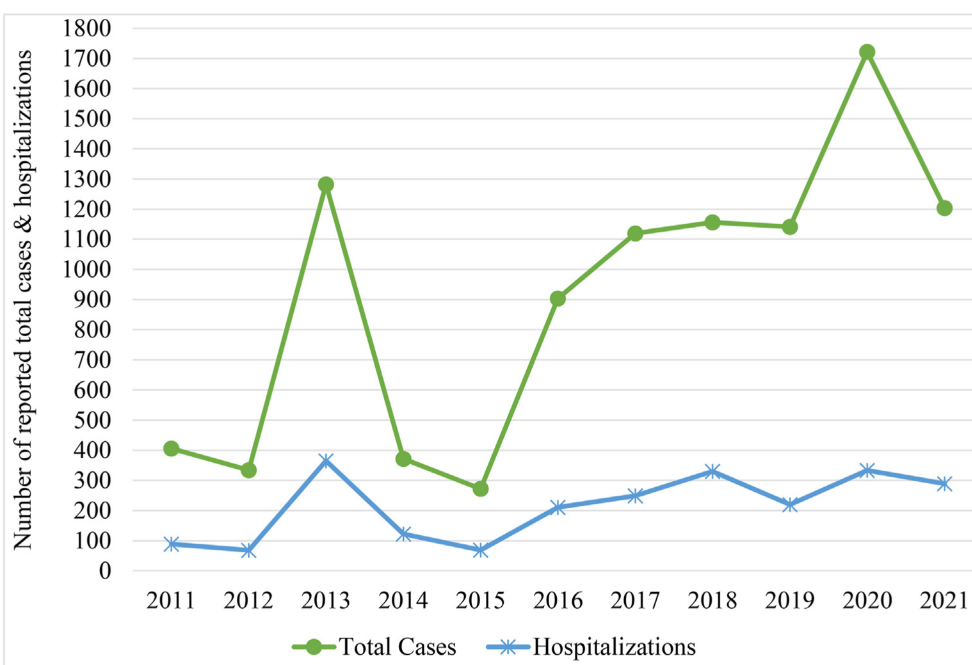

Figure 1. Total number of reported *Salmonella* infected cases & hospitalizations linked to poultry. The total number of reported *Salmonella* infected cases & hospitalization linked to live poultry and poultry products in each year during the past decade.

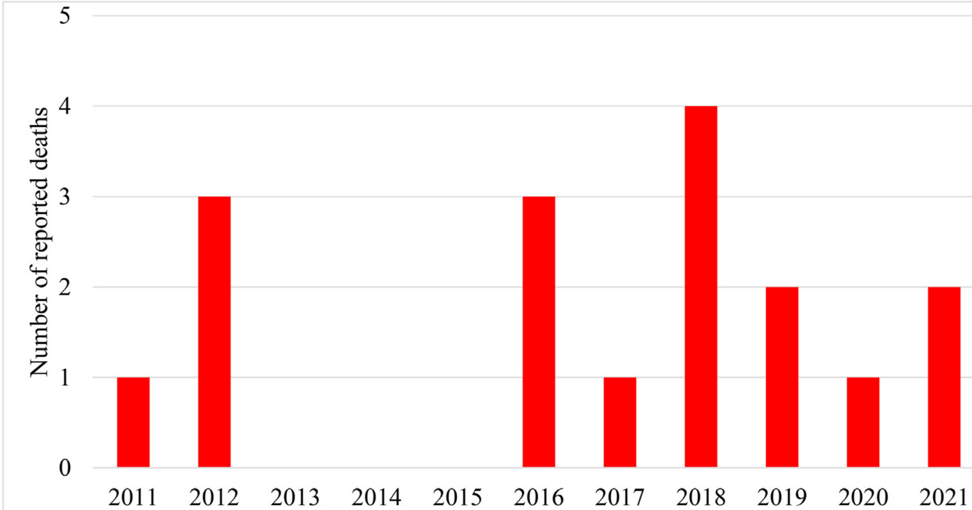

Figure 2. Total number of reported deaths due to *Salmonella* outbreaks linked to poultry. The total number of reported deaths due to *Salmonella* outbreaks linked to live poultry and poultry products in each year during the past decade.

in 358 cases and 133 hospitalizations including one death. This outbreak was responsible for the greatest number of poultry product related illnesses in 2018. In total, 314 isolates of *Salmonella* Reading possessed genes that predict decreased susceptibility or resistance to some or all of the following antibiotics: ampicillin, ciprofloxacin, fosfomycin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole (CDC, 2018f). Meanwhile, 334 people were infected with other types of *Salmonella* including *Salmonella* Enteritidis, *Salmonella* Indiana, *Salmonella* Infantis, *Salmonella* Litchfield, *Salmonella* Montevideo, and *Salmonella* Seftenberg. Though 56 people were hospitalized, there was no death. Twenty-eight isolates contained genes that predict resistance to at least one of the following antibiotics: ampicillin, amoxicillin-clavulanic acid, cefoxitin, ceftriaxone, ciprofloxacin, fosfomycin, gentamicin, streptomycin, sulfamethoxazole, and tetracycline. Multidrug-resistant *Salmonella* Infantis isolated in 2018 was linked to various raw chicken products, which resulted in 129 cases with 25 hospitalizations. A common source of contamination was not identified and the strain might be widespread in the chicken industry in the U.S. The strain of *Salmonella* Infantis in this outbreak was resistant to ceftriaxone, ciprofloxacin, or other antibiotics including ampicillin, chloramphenicol, fosfomycin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole. But it was susceptible to azithromycin, amoxicillin-clavulanic acid, and meropenem (CDC, 2018c; CDC, 2018d). Again, *Salmonella* Typhimurium infected 265 people and it led to 94 patients being hospitalized and one reported death in 2018. The source of contamination was identified as chicken salad. Fifteen clinical isolates contained genes for resistance to some or all of the following antibiotics: amoxicillin-clavulanic acid, ampicillin, cefoxitin, ceftriaxone, gentamicin, streptomycin, sulfamethoxazole, and tetracycline (CDC, 2018g). Meanwhile, 25 people were infected and 11 hospitalizations occurred due to an outbreak of *Salmonella* I4,[5],12:i:- in 6 states in 2018. Kosher chicken products were the source of contamination, but there was no resistance to antibiotics (CDC, 2018e). In the same year, a *Salmonella* Braenderup outbreak occurred infecting 45 people and resulting in 11 hospitalizations linked with Rose Acre Farms shell eggs. The strain was susceptible to antibiotics tested (CDC, 2018b).

In 2019, many people became sick after contact with poultry due to *Salmonella* Agona, *Salmonella* Alachua, *Salmonella* Altona, *Salmonella* Anatum, *Salmonella* Braenderup, *Salmonella* Enteritidis, *Salmonella* Infantis, *Salmonella* Manhattan, *Salmonella* Montevideo, *Salmonella* Muenchen, *Salmonella* Newport, and *Salmonella* Oranienburg. A total of 1134 people claimed that they had contacted chicks or ducklings throughout the U.S. (49 states) which eventually resulted in 219 hospitalizations and two deaths. Predicted antibiotic resistance was revealed through WGS in 814 isolates from ill people and 38 isolates from food, animals, or the environment. A total of 187 isolates were resistant to one or more of the following antibiotics: amoxicillin-clavulanic acid, ampicillin, cefoxitin, ceftriaxone, chloramphenicol, ciprofloxacin, fosfomycin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole. The majority of isolates (78%) did not show any resistance to the antibiotic. The other reported outbreak in 2019 was *Salmonella* Schwarzengrund linked to ground turkey. Seven infected people, one hospitalization, and no deaths were reported. But the strain was resistant to the following antibiotics: ampicillin, gentamicin, streptomycin, sulfisoxazole, and tetracycline.

The largest outbreak in history, related to poultry occurred in 2020 linked to backyard poultry. A total of 1,722 people infected, 333 hospitalizations, and one death were reported from the entire U.S. due to infection of multiple strains of *Salmonella* including *Salmonella* Agona, *Salmonella* Anatum, *Salmonella* Braenderup, *Salmonella* Enteritidis, *Salmonella* Hadar, *Salmonella* I4,[5],12:i:-, *Salmonella* Infantis, *Salmonella* Mbandaka, *Salmonella* Muenchen, *Salmonella* Newport, *Salmonella* Thompson, and *Salmonella* Typhimurium. Epidemiological investigation revealed that the infected people had contacted chicks and ducklings. Majority of recovered isolates (51.6%) (n = 1643) were showed resistance to amoxicillin-clavulanic acid, ampicillin, cefoxitin, ceftriaxone, chloramphenicol, fosfomycin, gentamicin, streptomycin, sulfisoxazole, tetracycline, and trimethoprim-sulfamethoxazole. There was no antibiotic resistance predicted for 795 (48.4%) isolates through predicted antibiotic resistance.

A *Salmonella* Harder outbreak occurred in 2021 linked to ground turkey which resulted in 33 cases and 4 hospitalizations (CDC, 2021c). Another outbreak linked to *Salmonella Enteritidis* occurred with raw frozen breaded stuffed chicken products in 2021. A total of 36 infected people and 12 hospitalizations were reported within 11 states (CDC, 2021b). The latest outbreak related to backyard poultry was reported in 2021, resulting in 1135 cases, 273 hospitalizations, and 2 deaths. CDC has reported that 25% of infected patients were children younger than 5 years old. Furthermore, CDC has emphasized to the farmers to take extra precautions when children handle poultry (CDC, 2021a). A possible reason for the higher percentage of infected children is the covid-19 pandemic. Since schools were closed for a considerable period, children had a greater opportunity to be involved with backyard poultry in 2021.

The information gathered from the Centers for Disease Control and Prevention was analyzed and the total number of poultry-related cases and the number of hospitalizations were included in this review. Figure 1 shows a gradual increase in the total number of poultry related cases and the number of hospitalizations during the past decade. The number of reported cases was increased during the past decade, but the incidents were decreased after 2020. According to the Foodborne Diseases Active Surveillance Network (FoodNet), the overall incidence of *Campylobacter*, *Salmonella*, STEC, and *Vibrio* infections, decreased during 2020 compared with the previous 3 years (average incidence for 2017–2019) in the FoodNet's surveillance area (15% of the U.S. population). The widespread of SARS-CoV-2 likely contributed to decreasing the foodborne illness due to lifestyle changes of consumers including frequent sanitizing, limited gathering and traveling, healthcare-seeking, and restaurant closures (CDC, 2021e). Figure 2 shows the number of reported deaths linked to poultry during the last decade. The year 2018 showed the largest number of deaths that occurred during the past decade due to *Salmonella* infections linked to poultry. A possible reason for the gradual increase of hospitalizations and higher number of deaths may be the increased resistance to antibiotics or decreased susceptibility to antibiotics of infected *Salmonella* strains. Figure 3 shows the number of reported *Salmonella* serovars linked to live poultry and poultry products in each year during the past decade. The number of *Salmonella* serovars has been gradually increased up to 2020 and only six serovars were responsible for *Salmonella* infections that were occurred in 2021 linked to poultry.

4. The prevalence of antimicrobial resistance of *Salmonella* in the U.S.

According to NARMS the prevalence of *Salmonella* has declined to approximately 6% within 14 years from 11.5% and 9.7% in retail ground turkey and chicken respectively (FDA, 2017). Multidrug Resistant (MDR) *Salmonella* was higher in isolates recovered from retail ground turkey (36%) versus retail chicken (20%). AMR *Salmonella* isolates from turkey (46.7%) had a higher resistance to at least 3 antimicrobial classes compared to chicken (14.6%) sampled via the cecal route (FDA, 2014). *Salmonella* has exhibited resistance to multiple antibiotics in every class/subclass of antibiotics including aminoglycosides, aminopenicillins, β-lactams, cephalosporins (third-generation) cephamycins, phenicols, and tetracycline (Mazengia et al., 2014). Multidrug Resistance (MDR) among human *Salmonella* isolates has remained consistent from 2008 to 2014 at 9.3%.

The production method may have an impact on the contamination of poultry products. Establishments not using antibiotics or identified as organic have a higher prevalence of *Salmonella* recovery whereas establishments using conventional methods have a lower recovery but more isolates resistant to two or more antibiotics (Cui et al., 2005; Lestari et al., 2009; Mazengia et al., 2014). Lestari et al. (2009) noted conventional isolates had higher resistance rates to gentamicin, kanamycin, amoxicillin-clavulanic acid, ceftiofur, cefoxitin, and chloramphenicol; organic carried higher resistance to streptomycin, trimethoprim-sulfamethoxazole, and tetracycline. A study by Sapkota et al. (2014) sampled *Salmonella* from poultry litter, water, and feed samples from conventional poultry houses that transitioned from conventional to organic and found that organic houses had significantly less AMR and MDR *Salmonella* isolates.

The predominant *Salmonella* serotypes recovered from chicken were Kentucky, Enteritidis, Typhimurium, Infantis, and Heidelberg (Nde et al., 2006; Parveen et al., 2007; USDA-FSIS, 2014). The predominant serotypes recovered from turkeys were Reading, Kentucky, Agona, Hadar, and Ouakam (USDA-FSIS, 2014). The most common *Salmonella* serotypes causing human infections are Enteritidis, Typhimurium, Newport, I4,[5], 12:i:-, Javiana and Heidelberg (CDC, 2016d). Regardless of the source (conventional or organic), *Salmonella* Heidelberg had higher resistance to two or more antibiotics (Mazengia et al., 2014).

Ceftriaxone is commonly used to treat salmonellosis, and 11.1% of turkey *Salmonella* isolates and 8.7% of cecal chicken *Salmonella* isolates were resistant to ceftriaxone in 2014 (FDA, 2014). The most common *Salmonella* serotypes resistant to ceftriaxone are Typhimurium, Newport, Dublin, Heidelberg, and I4,[5],12:i:- (CDC, 2016d). The report of Antibiotic Resistance Threats in the U.S. in 2019 showed that the resistance to ceftriaxone in nontyphoidal *Salmonella* is on the rise and approaching 10% for ciprofloxacin in 2017 (CDC, 2019d). Ceftriaxone is found in the Extended-Spectrum Cephalosporins (ESCs) antimicrobial class. ESCs are β-lactam antibiotics that interfere with the metabolism of cell wall synthesis (FDA, 2014; Seiffert et al., 2013). Bacteria have adapted and have developed resistance to the β-lactams by synthesizing β-lactamase, which cleaves the β-lactam ring and inactivates the antibiotic (Bae et al., 2015). The common β-lactamase genes associated with *Salmonella* resistance are bla_{TEM}, bla_{SHV}, bla_{CMY}, $bla_{CTX\text{-}M}$, and $bla_{OXA\text{-}1}$. The bla_{CMY} and $bla_{CMY\text{-}2}$ genes are frequently recovered from *Salmonella* isolates collected from humans (Dunne et al., 2000; Folster et al., 2010; Sjolund-Karlsson et al., 2010, 2013). *Salmonella* serotypes Newport, Heidelberg, and Typhimurium are associated with bla_{CMY}-positivity (Sjolund-Karlsson et al., 2013).

Ciprofloxacin, another antimicrobial commonly used to treat severe cases of salmonellosis, resistance has been less than 2% since 1997 in

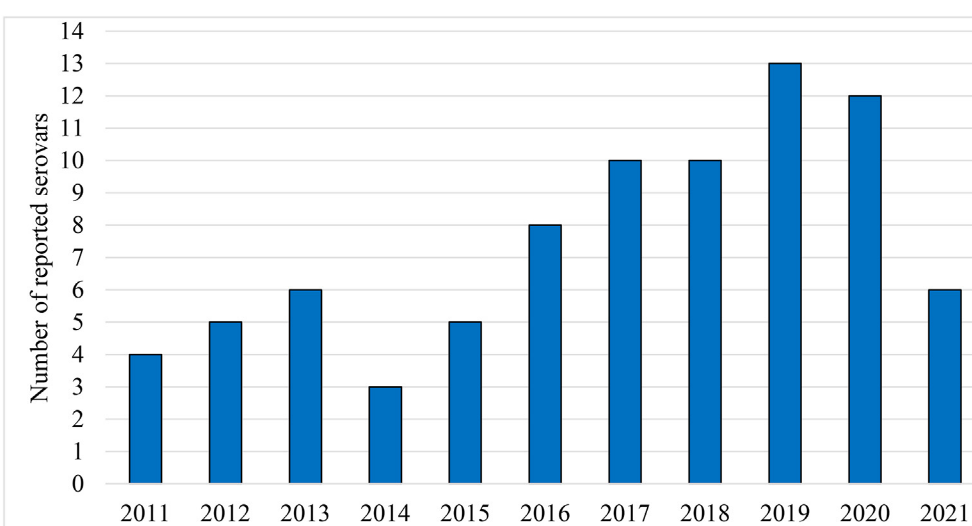

Figure 3. Total number of reported *Salmonella* serovars in each year linked to poultry. The total number of reported *Salmonella* serovars linked to live poultry and poultry products in each year during the past decade.

retail meat (FDA, 2014; Hur et al., 2012). Although rare, there have been cases documenting resistant strains for ciprofloxacin, which is part of the fluoroquinolone antimicrobial class (CDC, 2010; CDC, 2016d; Chen et al., 2007; Hur et al., 2012). Although not exceeding 4%, resistance to nalidixic acid has increased in human cases from 0.4% in 1996 to 3.5% in 2014 (FDA, 2014). This may be a cause for concern because nalidixic acid (a simple quinolone) is an indicator that correlates for the first of two mutations for full resistance to ciprofloxacin (CDC, 2016d; FDA, 2014). Bacteria gain resistance to nalidixic acid by plasmid mediation, which encodes transferable resistance to quinolones via the *qnr* gene. The *qnr* gene product directly protects the DNA gyrase from quinolone inhibition (Cavaco and Aarestrup, 2009; Irfan et al., 2012).

Salmonella Typhimurium DT104 has emerged as a public health threat that may be recovered from cattle, pigs, and chickens, particularly because it exhibits resistance to five antimicrobial agents (gene coding resistance): ampicillin (*bla*PSE-1), chloramphenicol (*floR*), streptomycin (*aadA2*), sulfamethoxazole (*sul1*) and tetracycline (*tet*[G]) (Boyd et al., 2001; Hur et al., 2012; Parveen et al., 2007; Rayamajhi et al., 2008). The genes responsible for MDR (Ampicillin, Chloramphenicol, Streptomycin, Sulfonamides, and Tetracycline (ACSSuT)), located on the chromosome in a region termed *Salmonella* genomic island (SGI1), can gain resistance to beta-lactam drugs, including ceftriaxone and amoxicillin-clavulanic acid and additional resistance to fluoroquinolones and higher generation cephalosporins (FDA, 2014; Hur et al., 2012; Mulvey et al., 2006). The incidence of the ACSSuT profile has declined in poultry from 1997 to 2014 (FDA, 2014).

Salmonella Heidelberg isolates have been recovered from food, processing environments, and cases of human salmonellosis. Compared to other non-typhoidal *Salmonella* strains, *S.* Heidelberg is commonly associated with more invasive human diseases and has become clinically significant due to the increase in the prevalence of MDR (i.e., β-lactams, aminoglycosides, chloramphenicol, sulfamethoxazole, tetracycline, streptomycin, kanamycin) and resistance to third-generation cephalosporins (Lynne et al., 2009; Shah et al., 2016; Zhao et al., 2008). The *S.* Heidelberg isolates, associated with the ground turkey outbreak in 2011, carried a new virulence plasmid encoding VirB4/D4 type IV secretion system (Folster, 2012; Gokulan et al., 2013). The VirB4/D4 type IV enhances the ability of *S.* Heidelberg to invade and persist in macrophages and intestinal epithelial cells. The regulation of the secretion system genes upon entrance into the macrophages and the impact of plasmid acquisition on survival may preclude that the T4SS is an important trait to enhance the virulence of the organism. The virulence is highly due to the modulation of the host immune response because the plasmid containing strains downregulate multiple members of the antimicrobial peptide pathways which are associated with limiting killing by the immune system components (Gokulan et al., 2013).

5. Monitoring of usage of antibiotics

The FDA monitors antimicrobial resistance among enteric bacteria in retail meats and establishes tolerances for veterinary drugs and action levels for food additives and environmental contaminants (CDC, 2016a; USDA-FSIS, 2016). Due to the high risk of antimicrobial resistance, in December 2013, the FDA published guidance #213 to limit the use of antibiotics for increased rate of weight gain and improved feed efficiency (FDA, 2013a,b). The FDA made a stand to promote the use of on-farm antibiotics solely for treatment, control, and prevention of specific diseases to ensure animal health. When an antimicrobial treatment is necessary to control or prevent a disease, these antimicrobials should be administrated optimally under the supervision of a licensed veterinarian (FDA Center For Veterinary Medicine, 2018). In addition, the products from livestock and poultry treated with antibiotics must no longer be sold under the label of "antibiotic-free" or "organic" (Livestock Health Care Practice Standard, 2022; USDA-FSIS, 2019). Starting January 2017, over-the-counter (OTC) animal drugs and animal drug combinations used by a layperson have been discontinued. Veterinarians are required to write veterinary prescriptions (Rx) or veterinary feed directives (VFD) for medically important antibiotics for specific diseases. Once the farmer obtains the prescription from a distributor that is registered with the FDA, all parties (veterinarian, farmer, and distributor) are required to file paperwork for a minimum of two years (FDA, 2013b). Antibiotics have been administered to livestock through feed and drinking water since 1946 and before 1993, the majority of antimicrobial drugs were approved for OTC purchase (Boyd, 2001; FDA, 2013b). Due to the overwhelming scientific studies and AMR bacteria outbreaks, the transition of requiring stricter veterinary oversight is a redundant step in the right direction. A final rule issued by the FDA requires distributors to provide estimates of sales categorized by specific species (cattle, swine, chickens, and turkey) to aid the U.S. government in a better understanding of how antimicrobials are sold and distributed for use on livestock (FDA, 2020). Effective July 11, 2016, this report must be submitted annually.

Although the FDA primarily determines which antibiotics are safe for use in livestock and appropriate conditions of use, the USDA samples meat, poultry, and egg products for antibiotic residues under the U.S. National Residue Program (NRP). For nearly two decades, the USDA has been proactive in surveillance, basic and applied research, education, and outreach to monitor levels of AMR (USDA, 2014). The NRP, which falls under the FSIS, identifies, ranks, and analyzes chemical contaminants in meat, poultry, and egg products. The areas of high public health concern include approved and unapproved veterinary drugs, pesticides, and environmental contaminants that may appear in FSIS regulated products. The aim of the NRP is to provide a process for identifying and evaluating chemical compounds used in food animals, analyze chemical compounds of concern, collect, analyze and report results and identify the need for regulatory follow-up subsequent to the indication of violative levels of chemical residues (USDA-FSIS, 2016).

Recently actions have been taken by the FDA to reduce the incidence of AMR bacteria caused by antibiotics. The FDA has the right to prohibit "extralabel" usage of certain drugs in livestock that may cause a risk to human health or lead to antimicrobial resistance. Extralabel is the "actual use of a drug in an animal in a manner that is not in accordance with the approved labeling" (ECFR, 2020). In 2012, the FDA prohibited certain uses of the cephalosporin class of antimicrobial drugs in cattle, swine, chickens, and turkey for growth promotion and disease prevention. When the prohibition was issued in 2009, the use of ceftriaxone (class of cephalosporins) resistance of *Salmonella* isolated from poultry and humans sharply declined from 38% to 18%, from 2009 to 2014. Cephalosporins are traditionally used in humans to treat pneumonia, skin, soft tissue infections, pelvic inflammatory disease, diabetic foot infections, and urinary tract infections. When cephalosporins are not effective against these diseases antimicrobials are provided with greater side effects. Other drugs in the cephalosporin class such as cephapirin and ceftiofur are not considered to cause significant antimicrobial resistance and may be administered by veterinarians to cattle, swine, chickens, or turkeys as indicated on the label (FDA, 2015). Fluoroquinolone, a separate antimicrobial class, has restrictive use in livestock as well. Fluoroquinolones are prohibited for use in poultry water. It has been determined, fluoroquinolones may cause fluoroquinolone-resistant *Campylobacter* species in poultry and be transmitted to humans (FDA, 2019b).

6. Conclusion

Salmonella infection is a serious health concern that causes fatal illness among people of all ages in the U.S. Poultry is known to be the main reservoir for this zoonotic pathogen. *Salmonella* is widespread in the environment and cannot be eliminated from the environment because of its heat, acid, and antibiotic resistance. The reported cases and hospitalizations due to *Salmonella* outbreaks linked to poultry have been increasing until 2020 and declined in 2021 because of frequent usage of sanitizers, restaurant closures, and limited traveling and gathering during the SARS-CoV-2 pandemic situation. Moreover, the total number of detected *Salmonella* serovars also declined by 6 in 2021 compared to 2019. Antimicrobial resistance of bacteria is a common defensive mechanism for microorganisms to survive in stressful environmental conditions. Bacteria resistance to antibiotics has been evolving up to today even before humans' existence on the earth because antimicrobials are not only human-made but also naturally originated such as bacteriocins, plant derivatives such as essential oils, etc. Antibiotics including ciprofloxacin, ceftriaxone, and azithromycin are commonly used to treat patients with severe *Salmonella* infections. *Salmonella* has been developing resistance to these antibiotics and it can be a challenge to treat *Salmonella* infections and will have higher hospitalization rates. Antibiotic resistance threats in the U.S. 2019 reported that extensively drug-resistant (XDR) *Salmonella* Typhi is resistant to all tested antibiotic classes but not for classes macrolides and carbapenems. The antibiotics that belong to macrolides and carbapenems classes are more effective to treat diseases caused by XDR *Salmonella* Typhi. Because of increasing AMR in *Salmonella*, few antibiotics are available to treat the patients with severe infections.

Controlling AMR is not a simple process that can be achieved overnight. Rules and regulations must be implemented to control the overuse/misuse of antibiotics by regulatory agencies. Reduction of usage of antibiotics in animal husbandry is crucial. The FDA must continue to monitor the effect of the restrictions placed on the use and sale of antibiotics for food-producing animals. Additional research is needed on the prevalence, enumeration, AMR gene transferring (vertical and horizontal) along the food supply chain including processing lines to better understand the controls and production methods establishments have in place.

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The authors declare no conflict of interest.

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