Food Microbiology 53 (2016) 104–109

Contents lists available at ScienceDirect

Food Microbiology

journal homepage: www.elsevier.com/locate/fm

Review

Salmonella and *Campylobacter*: Antimicrobial resistance and bacteriophage control in poultry

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ARTICLE INFO

Article history:
Received 3 March 2015
Received in revised form
12 August 2015
Accepted 10 September 2015
Available online 11 September 2015

Keywords:
Chicken processing
Antimicrobial overuse
Salmonella
Campylobacter jejuni
Campylobacter coli

ABSTRACT

Salmonella and *Campylobacter* are major causes of foodborne related illness and are traditionally associated with consuming undercooked poultry and/or consuming products that have been cross contaminated with raw poultry. Many of the isolated *Salmonella* and *Campylobacter* that can cause disease have displayed antimicrobial resistance phenotypes. Although poultry producers have reduced on-the-farm overuse of antimicrobials, antimicrobial resistant *Salmonella* and *Campylobacter* strains still persist. One method of bio-control, that is producing promising results, is the use of lytic bacteriophages. This review will highlight the current emergence and persistence of antimicrobial resistant *Salmonella* and *Campylobacter* recovered from poultry as well as bacteriophage research interventions and limitations.

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1. The cost of *Salmonella* and *Campylobacter*

Salmonella and *Campylobacter* are major causes of concern for the poultry industry. Poultry, more specifically, chicken, is recognized as a major vehicle for *Salmonella* and *Campylobacter* (Guo et al., 2011; Domingues et al., 2012; Greig and Ravel, 2009; Newell et al., 2011; Hermans et al., 2012). Sold as either whole carcass, parts or ground meat, broiler chickens are the number one type of chicken sold in the United States and constitute a multi-billion dollar a year industry. According to the Unites States Department of Agriculture (USDA), in 2012, the broiler chicken industry grossed $24.8 billion nationwide, which was an 8% increase from 2011 (Usda-Nass, 2013). Considering *Salmonella* related infections cause an estimated $365 million in annual direct medical costs (CDC, 2011a) and basic *Campylobacter* cost was reported at $1.56 billion (Scharff, 2011); these two groups of bacteria have the potential to cause major financial and health concerns.

Salmonellosis is caused by ingesting *Salmonella* spp. Symptoms usually occur 12–72 h after consuming contaminated foods and last for 4–7 days. Although it is usually a self-limiting infection that typically does not require any antimicrobial interventions, children,

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http://dx.doi.org/10.1016/j.fm.2015.09.008

the elderly and those who are immune-compromised are at a higher risk for severe diarrhea that requires hospitalization. If not treated, more severe symptom can occur. The bacterium could mobilize from the intestine through the blood stream to other organs (septicemia) which could potentially be fatal (CDC, 2014b; Guo et al., 2011).

Campylobacter is one of the most prevalent causes of foodborne illness in the United States. These bacteria, more specifically, *Campylobacter jejuni* and *Campylobacter coli* species, infect approximately 2.4 million persons each year (CDC, 2011b). *Campylobacter* infections are not generally associated with outbreaks and tend to be sporadic occurrences, with symptoms including nausea, abdominal pain, fever and bloody diarrhea that can last for approximately seven days. If untreated in immunocompromised persons, the disease can spread to the blood stream and cause life threatening complications (CDC, 2014a). *Campylobacter* is a commensal organism that colonizes the gut of birds, and infections are usually associated with undercooked poultry and/or accidental cross contamination of raw poultry with ready-to-eat foods, such as fresh produce (CDC, 2014a; Abay et al., 2014). Traditional means to curb pathogenic infections during primary production included the supplementation of antimicrobials in animal feed, which leads to selective pressure and subsequently the development of resistant bacteria. This resistance makes treating infections with common antimicrobials less effective in both human and veterinary settings. As a result, alternative strategies to prevent and control infections in commercial poultry flocks is increasingly becoming more necessary. One such method that has been gaining popularity is the use of bacteriophage therapy. The aim of this review is to examine the impact of antimicrobials on the farm that has led to antimicrobial and multi drug resistant *Salmonella* and *Campylobacter*, primarily focusing on chicken production as well as the potential use of bacteriophages as a source of biocontrol along the farm-to-fork pathway.

2. Threat of antimicrobial overuse and abuse in agricultural practices

Since penicillin was introduced in the 1940s, antimicrobials have reigned supreme as a means to prevent, protect and defend against infections in both humans and animals, especially in Western cultures. Antimicrobials have traditionally been placed in the feed of agricultural animals as a means to prevent infections amongst intensively farmed poultry and livestock. A side effect of this practice was the promoted growth and performance of the animal, both desirable animal husbandry traits. One study showed a link between antimicrobials used as a growth promoter and diminished bile salt hydrolase activity, a gut-bacteria produced enzyme. This subsequently caused an increase in the host's lipid metabolism and, consequently, growth (Lin, 2014). Sub-therapeutic and overuse of antimicrobials in human and animal therapy and feed have been linked to the increased antimicrobial resistance observed worldwide (WHO, 2014). Each year, at least two million people in the United States are infected with bacteria that are resistant to at least one of the drugs designed to combat it, and approximately 23,000 individuals die as a direct result (CDC, 2013).

Sub-therapeutic administrations have given rise to development of resistance to antimicrobials that were not used on the farm (Varga et al., 2009a, 2009b; Zhang et al., 2009). Antimicrobial resistant and bacteria have even been isolated in areas where antimicrobials were prohibited and had not been administered. For example, Kazimierczak et al. (2009) was able to isolate tetracycline resistant bacteria from the gut of pigs raised on USDA-certified organic farms. Considering that the use of antimicrobials on the farm was prohibited and the mother of the pigs was also born on the antimicrobial free farm, the source of the multiple drug resistant (MDR) bacteria remained unknown (Kazimierczak et al., 2009).

Ceftiofur is a third generation cephalosporin, an antimicrobial that is structurally related to penicillin, which has a <beta>-lactam ring that obstructs bacterial cell wall formation and has been approved for use in feed animals in the United States. The bla_{cmy} gene is responsible for encoding the enzyme cephalomycinasecodes, which reduces susceptibility to first, second and third generation cephalosporins. Organisms that possess the bla_{cmy} genes not only had resistance to antimicrobials commonly used on the farm, like ceftiofur, but also showed a resistance within the penicillin class of antimicrobials commonly used to treat people (Bogaerts et al., 2011; Johnson et al., 2010). Mohamed et al. (2014) isolated 309 *Salmonella* Typhimurium and *S.* Kentucky strains from chicken carcasses during pre- and post-chill tank poultry processing and tested these isolates for resistance to ceftiofur. Of those 309 isolates, 145 isolates were positive for bla_{cmy} genes. Theoretically, if an individual were to become infected with a bacterial isolate that harbored the bla_{cmy} gene, treatments with penicillin and/or ceftiofur class of antimicrobials with <beta>-lactam rings could prove to be less effective.

Several studies also indicate that *Campylobacter* isolated from poultry expressed phenotypic patterns of MDR. Abay et al. (2014) randomly isolated 200 *C. jejuni* strains from 100 patients that were positive for *Campylobacter* infections and 100 from chickens purchased at retail. All isolates were tested against nine antimicrobials and both human and chicken isolates were found to have resistance to at least one antimicrobial with a 92% and 96% occurrence, respectively, and 85% and 94% showed resistance to two or more antimicrobials, respectively. The most common resistance combination observed was to ciprofloxacin, enrofloxin, nalidixic acid, and/or tetracycline. Perez-Boto et al. (2012) isolated 430 *Campylobacter* strains from the caeca of chickens raised on two different farms. Of those isolates, 68.5% were resistant to quinolones, 46.5% displayed tetracycline resistance and 9.6% were resistant to amoxicillin, a <beta>-lactam class of antimicrobial. In the United States, broiler feeds were supplemented with quinolones and fluoroquinolones from 1995 to 2005. Although the incorporation of these compounds in animal feed was outlawed in 2005 and their usage has drastically diminished since then, a joint multi-state study conducted by Johns Hopkins Bloomberg School of Public Health and Arizona State University found fluoroquinolones in feather meal which is a common supplement in chicken, cattle, and swine feeds (Johns Hopkins University Bloomberg School of Public Health (2012)).

It has been suggested that quinolone use in the poultry industry led to the resistance phenotype observed in pathogens (Waters et al., 2011). Resistance to first, second and third generation quinolones are coded by the qnr gene within class-I integrons located on transposons, plasmids, and/or chromosomes. Quinolone are commonly used to treat nosocomial and other clinical infections (Bliziotis et al., 2011). Treatments of these infections could become complicated if the bacteria possessed the qnr gene. Recently, several studies reported that the reduced sub-therapeutic use of antimicrobials on farms in turn reduced the number of resistant pathogens recovered, however, resistance to multiple drugs still persists and alternative means of control must be considered (Alali et al., 2010; Van Kessel et al., 2012; Dersjant-Li et al., 2014; Santini et al., 2010; Ruddat et al., 2014). One method of pathogenic biocontrol that has shown to be a promising alternative to synthetic antimicrobials is the use of bacteriophages.

3. Bacteriophages: A virus to control bacteria

The therapeutic use of bacteriophages (phages) to combat bacterial infections dates back to the early 20th century (Garcia et al.,