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Antibiotic Resistance in Campylobacter

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doi: https://doi.org/10.57709/35488205

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ABSTRACT

Antibiotic Resistance in Campylobacter is a growing global health concern, especially among vulnerable populations. Contamination and infection often start in food production, when meat is slaughtered and bacteria have time to grow, or in water contamination from wastewater runoff that is not adequately treated before consumption. When severe infection occurs, antibiotics are administered to assist with recovery. These antibiotics fall into five classes with the addition of multi-drug-resistant fluoroquinolones, macrolides, tetracyclines, aminoglycosides, and beta-lactams. Each antibiotic has a specific property to combat campylobacter. However, they also have specific resistant mechanisms, such as a genetic mutation, that allow resistance. This Systematic Review seeks to evaluate the status of antibiotic resistance.

Antibiotic Resistance in Campylobacter

By

Adrienne Clewis

May 2023

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A Thesis Submitted to the Graduate Faculty

of Georgia State University in Partial Fulfillment

of the

Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

30303

Author's Statement Page

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May 2023

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Introduction

Increased antibiotic use has accompanied the growth of several antibiotic-resistant bacteria in Campylobacter. The properties of this bacteria have evolved in both food production environments and the community and fostered resistance to available drugs. Campylobacter species are gram-negative, spiral-shaped, "S"-shaped, or curved, with a flagellum single polar, bipolar, or no flagellum, depending on the species. Campylobacter species are non-spore-forming, vary in size from 0.2 to 0.8 by 0.5 to 5 m, and are chemoorganotrophs, amino acids, or tricarboxylic acid cycles (Ahtesham et al., 2019). Twenty-six species, two provisional species, and nine subspecies (as of December 2014) are assigned to the Campylobacter genus. Not all species cause human illness; approximately 90% of human Campylobacter illness is caused by C. *jejuni* (subspecies *jejuni*) and C. *coli.* (cdc.gov). These species are thermotolerant and grow in microaerophilic conditions with an incubation period of 2-5 days from when the person is exposed to when they show symptoms (Sher et al., 2021).

The production and consumption of contaminated food containing bacteria are a pathway of human illness. Gastrointestinal tract infection presents in humans as bloody diarrhea, vomiting, abdominal cramps, and pyrexia. Contamination and infection often start in food production, when meat is slaughtered, and bacteria have time to grow during incubation periods or in water contamination from wastewater runoff that is not adequately treated before consumption. Foods at the highest risk include raw and undercooked chicken, turkey, and beef. Vegetables that have encountered contaminated wastewater may also carry the bacteria. Lastly, wastewater can encounter animal feces from local farms, wild birds, or even human sewage and enter lakes and streams during heavy rains and other weather conditions. If this water is not correctly treated, there i a risk of illness and if severe enough it may lead to hospitalization.

Many campylobacter species are known to cause gastrointestinal conditions, including inflammatory bowel diseases (IBD), Barrett's esophagus, colorectal cancer, Guillian barre syndrome, arthritis, and Miller Fisher syndrome if not adequately treated. According to Lui et al.,2022, the Czech Republic had the highest reported incidence of campylobacteriosis worldwide (215 per 100,000 in 2019), followed by Australia (146.8 per 100,000 in 2016) and New Zealand (126.1 per 100,000 in 2019).

A significant part of campylobacter persistence is its resistance to antibiotics. Antimicrobial resistance is a problem both in the U.S. and worldwide; for developed and developing countries. One of the reasons behind antimicrobial-resistant development is the usage of antibiotics in animal agriculture, including in poultry feed (Sher et al., 2021). In addition, the increasing and sometimes inappropriate use of antibiotics to treat human illness has also contributed to the resistance. Over the years, Campylobacter bacteria have become increasingly antibiotic-resistant, especially among children. There are five significant categories/classes of antibiotics to treat Campylobacter: aminoglycoside, beta-lactam, fluoroquinolone, macrolide, and tetracycline. Each of these antibiotics has been used within the medical field to combat symptoms and illnesses related to gastroenteritis. It is important to note that not every infection requires antibiotics; only those with severe illness may require antibiotics to assist with recovery (cdc.gov)

This systematic review aims to evaluate the status Campylobacter resistance of Campylobacter.

Research Question and Objective

This review seeks to answer how Campylobacter resistance to Campylobacter has changed.

Methods

Study Design

Following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA), this systematic review was performed on reviews and cohort studies focusing on Campylobacter resistance in Campylobacter.

Search Strategy

The Cochrane Library for Literature, Google Scholar, Galileo, Molecular Diversity Preservation International (MDPI), and PubMed were systematically searched without language or geographic restrictions. Different combinations of terms were used, such as "antibiotic resistance of campylobacter" OR "campylobacter" and "campylobacter resistance" OR "antimicrobial resistant campylobacter OR "antibiotic campylobacter" OR "C. jejuni" and "C.coli ." The reference lists of all articles identified were screened as well.

Data Extraction

For each study, the following information was extracted: first author name, year of publication, country, study design, study period, participant characteristics, outcomes, outcome assessment, and the number of antibiotic-resistant campylobacter cases.

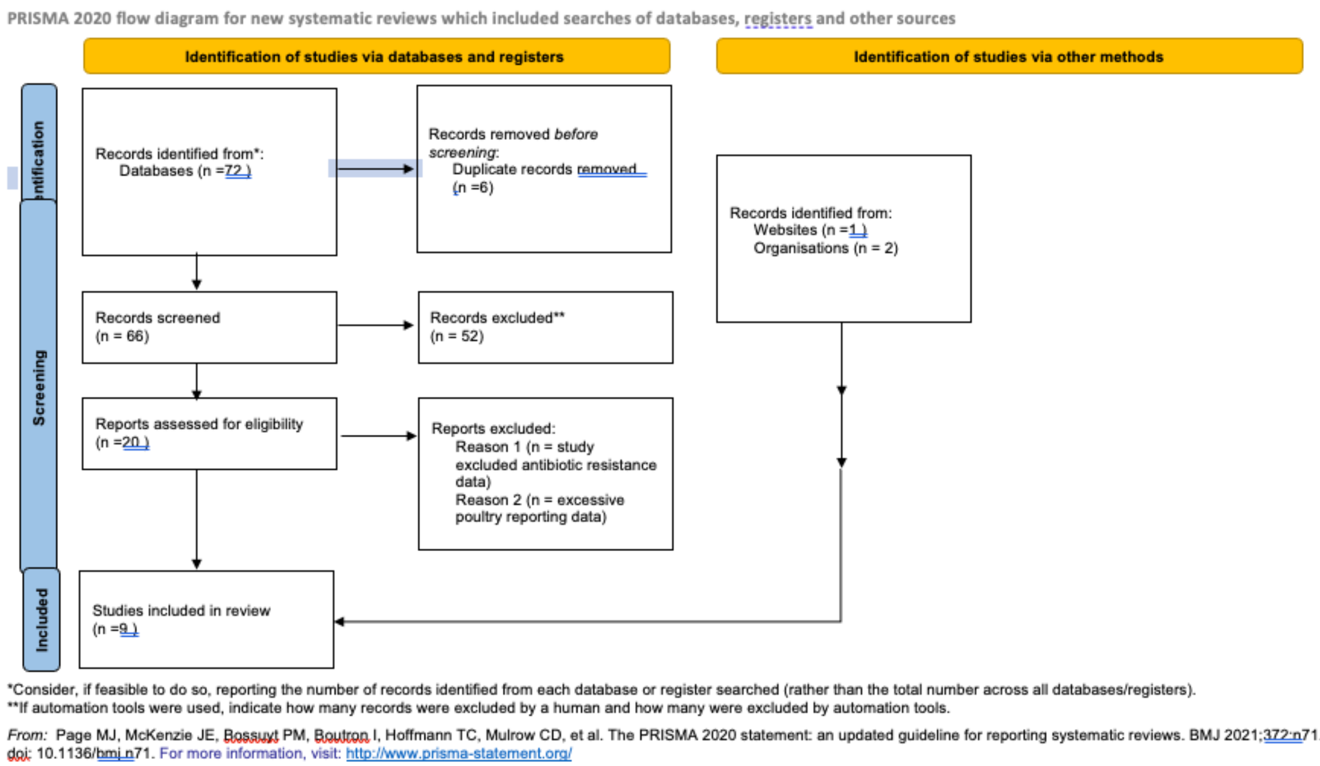
Results

Study Selection

Databases were searched from 2007 to the present, emphasizing studies from 2013 to 2023. Both the titles and abstracts of the search results were screened. The remaining abstract and full text of the articles were assessed for eligibility. Studies were included if they were reviews and cohort studies, systematic reviews, meta-analyses, and Cross-sectional studies. Studies were excluded if they were clinical trials, article books, and documents and did not report on campylobacter antibiotic resistance outcomes. Studies that included vaccination trials were also excluded. Studies that included human subjects were preferred, animal studies were not ruled out, and studies that included animals and humans were included.

A database search identified a total of 72 articles reported antibiotic resistance of Campylobacter. Studies that reported on antibiotic resistance in humans versus in livestock or chickens were sought after. 6 Duplicate studies were removed before the initial study screening. Fifty-two studies were excluded after the review of the title and abstracts confirmed that they were not relevant to the topic or excluded information from the review; examples include studies that focused on dogs(pets), strong focus on water, different bacteria, or solely on treatment. Twenty articles were assessed for their eligibility for inclusion, excluding another 11 studies, primarily due to excessively repetitive information on animal antibiotic resistance instead of human, articles focused on food production safety, and articles focused on molecular genetics in poultry production.

Eight studies were identified to meet the criteria. An additional 1 article from websites and organizations to create a total of 9 articles included in the final systematic review



Study Characteristics

This systematic review includes nine studies published between 2007 and 2023 reporting antibiotic resistance and Campylobacter. Three studies antibiotic resistance in Campylobacter (species, *jejuni*, and *coli*) in children ages five and under by collecting and analyzing stool samples (Schiaffino et al., 2019) (Szczepanska et al., 2017) (Noreen et al., 2019). In the study by Noreen et al., 150 diarrhea samples were collected from children. Eighty-two of these samples were positive for C. *Jejuni*, and compared to reports from the earlier years, results showed an increase in prevalence (11-29% previously reported to 54%) and increased rates of resistance to antibiotics.

Another studies evaluated Campylobacter *jejuni* antibiotic-resistant genes in poultry meat samples (Khan et al., 2021). This study evaluated antibiotics to specific targeted antibiotic-resistant genes found in poultry meat and tissue samples. Fifteen different antibiotics were tested in an antimicrobial susceptibility test. Significant antibiotic-resistance genes were targeted using specific primers, PCR amplifications, and conditions. The sample regions were important in which antibiotics were more resistant than others. The highest antibiotic resistance was found against Amoxicillin ((3%) and the least among Gemifloxacin (8%). As for the antibiotic-resistant genes (ARG's), blaTEM lead at (93%) and AADB at least (9%).92% of isolates were found to have multiple antibiotic resistance.

Among the published reports on Campylobacter antibiotic resistance of Campylobacter, each classification of antibiotic is put into five classes and evaluated on its attribution to resistance, possible gene and DNA mutations, and the antibiotic properties (Iovine, 2013) (Alfredson et al., 2007) (Shen et al.,2017). They note the correlation between animal resistance strains and increased resistance in humans. Another noteworthy attribute is that countries that have stopped using antibiotics for veterinary purposes, particularly Fluoroquinolones, have the lowest levels of resistance and reported cases. Australian data report 2% resistance for humans and from broiler farms. Danish data depicts 11% from their poultry compared to 57 %from imported meats, and Norway is also on the lower end, with 6.7% reported

The reviews explained that fluoroquinolone works by disrupting DNA replication. There are two main enzymes attributed to cell replication: DNA Gyrase and Topoisomerase 4. Fluoroquinolone binds to DNA Gyrase and DNA, stabilizing the DNA complex. This action results in breaks in the DNA that are fatal to the bacteria a. This is the primary source of resistance. The resistance occurs at a single point mutation located on the gyrase gene, resulting in fluoroquinolone resistance.

A common trend found among all these studies was that the class of Fluoroquinolones antibiotics has decreased in their usefulness, and macrolide resistance remains steady. Many of the isolates showed resistance to ciprofloxacin, while the least frequently reported antibiotic resistance was among azithromycin. Campylobacter-induced illness was associated between foods (Poultry) and surface water; the lowest sources of campylobacter isolates were found in domestic pets, particularly dogs. C. *jejuni* bacteria possessed the highest antibiotic-resistant rate in the campylobacter species across all antibiotic treatments.

Results of Individual Studies

Research Table					
Title	Study Design	Author, Year	Participant, if any	Outcomes	Comments
Transmission of multidrug-resistant *Campylobacter jejuni* to children from different sources in Pakistan	Cross-Sectional	Noreen et al. 2019	150 Human stool sample. Children ages 2-5yrs old	Of the 150 samples collected, 82 were positive for *C. jejuni*. Overall, 75% of the samples were resistant to more than eight of the thirteen antibiotic s. This study also found a higher resistance to antibiotics among poultry than what was previously reported.	Due to lack of surveillance program, underdeveloped countries have underreported the prevalence of multi drug resistant isolates of C. jejuni.
Antibiotic Resistance of Campylobacter Species in a Pediatric Cohort Study	Cohort	Schiaffino et al. 2019	303 patients followed until 5years of age	A total of 10008 stool samples from asymptomatic children and 3175 samples from children with diarrhea between March 2010 and February 2016. 242 children	

				(979.9%) tested positive for Campylobacter. The most effective oral antibiotic was amoxicillin and clavulanic acid. The highest level of resistance was noted among ciprofloxacin; 77.4% *C.jejuni* and 79.8% non *C.jejuni*. The age at when the children presented with their first diarrhea ciprofloxacin resistant isolate was 12-months and 18-months for azithromycin.	
Prevalence and antimicrobial resistance in Campylobacter *jejuni* and Campylobacter *coli* isolated from children and environmental sources in urban and suburban areas	Cross-Sectional	Szczepanska et al. 2017	Stool samples from 1020 children ages 0-4yrs old. 433 samples of poultry meat. Rectal swabs of 260 domestic pets	This study takes place over a period of 3 years. Of the 3 categories, poultry meat had the highest prevalence of Campylobacter (33.3% in 3 years) with the lowest being among dog (6.2%). The prevalence among	

			2weeks-24 months old. 250 water samples	children was 9.6% with changes over the course of 3 years. The lowest antimicrobial resistance rate found within gentamicin and azithromycin. High rates of ciprofloxacin resistance were noted in all isolates across the board. Resistance to two or more antimicrobials were found in 40% of *C.jejuni* and 29% of *C.coli* isolates for all samples	
New and alternative strategies for the prevention, control, and Campylobacter antibiotic-resistant *Campylobacter*	Review	Dai et al. 2020		In the review of antibiotic resistance, a unique feature of fluoroquinolone was noted; campylobacter increased prevalence in the absence of antibiotic use. Macrolides became the first choice, however it's levels	

				of resistance have increase, especially in developing countries. Considering recent resistance, this review notes other approaches to controlling Campylobacter such as prebiotic and probiotics. While there is still a need for further studies to be completed both options have shown to effectively control infections in humans	
Distribution of Antibiotic Resistance and Antibiotic Genes in Campylobacter *jejuni* Isolates from poultry in Northwest of Pakistan	Cross-Sectional	Khan et al. 2020	1260 Poultry meat samples from Northwest Pakista n. 182 isolates from 4 regions varying in temperature and climate.	Overall prevalence of Campylobacter; Peshawar Division (21%), Bannu division (16%), Malakand Division (133%), and Hazara Division (8%).182 isolates were tested among 15 different antibiotics, the highest resistance was found	

				against Amoxicillin (93%) and least resistance against Gemifloxacin (8%). The highest antibiotic resistant gene was blaTEM (93%) while the least was aadb(9%). Each region had a portrayed different resistant gen e. 92% of isolates were found to have multiple antibiotic resistance.	
Antibiotic resistance and resistance mechanisms in Campylobacter *jejuni* and Campylobacter *coli*	Minireview	Alerdson & Korolik 2007		In the past decade, a rapidly increasing proportion of Campylobacter strains have developed resistance, particularly to Fluoroquinolone. However, in countries such as Australia, resistant strains remain low due to infrequent use of antibiotic s. Over time campylobacter has	

				natural transformed indicating resistant genes rapidly transferred between strains.	
Antimicrobial Resistance in Campylobacter spp	Review	Shen et al. 2018		This review focuses on the antibiotic resistant mechanism that have emerged in recent years as it pertains to each class of antibiotics. Each antibiotic has a specific purpose and treatment choice. Fluoroquinolones is used to treat bacterial disease in humans and animals by targeting two essential enzymes, DNA gyrase and topoisomerase IV, and impair DNA replication. Mutations in the genes are responsible for the resistance. Resistance to the class of Macrolide antibiotics occurs by	This review goes over a total of 9 antibiotic classes and their resistant mechanisms.

				three mechanisms: enzymatic inactivation of macrolides, modification /point mutations in the target, and enhanced drug efflux. Tetracyclines are widely used in both animal and human medicine. Due to its widespread use, this class of drugs has number of resistant determinants which is often mediated by one of the four mechanisms: efflux pumps, chemical modification, ribosomal protection proteins, and mutation in rRNA	
Resistance Mechanisms in Campylobacter *jejuni*	Review	Iovine 2013		This review focuses on antibiotic resistance mechanisms found in *C. jejuni* for 5 commonly used classes of antibiotics. The increase of	

				animal fluoroquinolone uses in food production led to resistant strains of campylobacter in animals. In correlation, there was an increase in resistant human infections.	
Antibiotic Resistance Threats in the United States	Report	CDC 2019		Drug resistant Campylobacter is listed as a serious threat by the C DC. This report acknowledges the One Health challenge; the people is connected to the health of animals and the environment. This report also breaks down resistance factors within vulnerable populations such as the young, old, and sick. Included in this report are the number of reported infections	This report includes multiple drug resistant bacteria and recommendations based on all concerns

				and death; 448,400 infections and 70 deaths.	

Discussion

The increasing rate of antibiotic resistance in Campylobacter has become a public health concern due to the difficulty with treatment among severe cases and the total global cost in health care. Campylobacter is a foodborne pathogen and, over the years, has evolved to become resistant to clinically important antibiotics such as Fluroquinolones and Macrolides. Our frequent misuse of antibiotics has resulted in resistance to bacteria worldwide. This misuse is within our medical facilities to treat disease and our food production and manufacturing yards. Resistance to antibiotics within the fluoroquinolone class of drugs has decreased its usefulness as a drug of choice among practitioners to treat campylobacteriosis, which has led to an increase in the following practical class of drugs, Macrolides (Alferson et al., 20 07). On the other hand, macrolide resistance, while it still occurs, occurs slowly, which has recently increased its usage in both veterinary and health practices.

The ability of Campylobacter to resist antibiotics has shown that the bacteria can adapt quite well. Data from these studies suggest an increase in antibiotic resistance to isolates. However, the most alarming factor; for children under 5, adapting means resistance to bacteria within the first 12-18 months of life (Schiaffino et al. 20 19). The cross-sectional studies show that the most vulnerable populations are also the most at risk; creating resistance in developing countries among young children only adds to the burden of resistance as adults. Overall, antibiotics in cases of campylobacter illness should be given to individuals 65 and up, pregnant women, and those with weakened immune systems. All others should be encouraged to intake more liquids for the duration of symptoms.

The literature shows the rise in antibiotic resistance and the ability of Campylobacter to adapt to antimicrobial usage. If we continue to use the same strategies in food production and illness treatment, we will see new antibiotic resistance emerging in Campylobacter. Many practitioners have recognized this same concern. Thus, the question is not "What is the problem" but rather "How do we fix it." This study gave light to a snapshot of the status of antibiotic resistance. However, it may have also provided insight into ways to move forward. When implementing new policies, we should focus our efforts on decreasing the use of antibiotics in our poultry process while also increasing our sanitation and storage processes (in water, seafood, and vegetation). Since most human infections are acquired through contact with these foods, our first line of defense should be strong. Our decrease should follow proper sanitation and storage in misuse and overuse of antibiotics to treat all humans. There are various other options to explore when treating a patient, including increasing liquids while symptoms persist. Globally, our surveillance programs on the issue should continuously be updated with samples taken and reported when applicable.

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