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Review Article

Campylobacter infections in Middle Eastern children: Review article

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ABSTRACT

Campylobacter jejuni (*C. jejuni*) infections among children have become an alarming challenge for developed and developing countries. This narrative review highlights the concerning situation of *Campylobacteriosis* and its antimicrobial resistance among Middle Eastern children. The review targeted studies on *Campylobacter* infections in the Middle East, focusing on those publications that were conducted within the past 14 years. The selected publications were sourced from the Google Scholar and PubMed databases. There was scanty published data addressing compylobacteriosis and its antimicrobial profile specifically among Middle Eastern children. Although there has been international concern about the role of *C. jejuni* and *C. coli* in causing childhood diarrhea, many regions in the Middle East do not appear to share the same level of concern. Furthermore, the complex interplay of socio-demographic and environmental elements that may influence *Campylobacter* infections, coupled with the globally rising concern over antibiotic resistance in *Campylobacter* spp (particularly multidrug-resistant strains), raises significant concerns in this region. Moreover, the presence of co-infections with *Campylobacter*, known to worsen disease severity, could exacerbate the issue and place a greater burden on healthcare systems. Additionally, the low awareness and insufficient prioritization of this public health issue, compounded by political conflicts in parts of the Middle East, present multiple challenges for children in several regions of the Middle East. These challenges, along with the consequences of late sequelae from *campylobacter* infection, put many children in this region at significant risk. To effectively tackle these challenges, critical targeted interventions must be implemented. These interventions include conducting comprehensive epidemiological studies to understand the burden of *Campylobacteriosis* in Middle Eastern children, characterizing the antibiotic susceptibility patterns of prevalent strains, updating healthcare practices to align with prevailing resistance profiles, adopting appropriate antibiotic prescription policies, and implementing robust infection control measures in this specific population.

1. Introduction

Campylobacter are gram-negative, flagellated bacteria that can cause zoonotic infections in both humans and animals. It poses a significant threat to human communities as it colonizes animal reservoirs and spreads through livestock feces, contaminating water sources, the environment, and the food chain.[1] Furthermore, it was demonstrated that the agents of *Campylobacter* infections possess several genes associated with pathogenicity and antibiotic resistance.[2] Each year, approximately 525,000 children under the age of five lose their lives due to diarrheal disease, making it the second prominent cause of death in

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children.[3] *Campylobacter* is widely recognized as a notable agent of acute diarrhea, particularly in individuals under the age of 5 and those who are 65 years old and above.[4] Moreover, concurrent infection with *C. jejuni* in symptomatic children has been shown to increase the severity of symptoms, and a higher risk of complications.[5] In addition, *C. jejuni* was demonstrated as gent of peritonitis among children in some instances.[6] The invasiveness of *C. jejuni* was linked to the possession of certain genetic elements that play an essential role in these types of infections.[7] The *Campylobacter* infection in children may be predicted by observing essential manifestations, such as a brief period of emesis, the presence of blood and mucus in their feces, and lower levels of Aspartate Transaminase.[8] *C. jejuni* infection has become increasingly prevalent worldwide over the last century, affecting both developed and developing nations with a particular impact on children.[9] This infection can occur as a result of multiple factors, such as exposure to natural reservoirs of *Campylobacter* like fowls and aquatic repositories, non-literate caregivers, and lack of proper personal sanitation.[10,11] The efficiency of immune system for infected group, dietary patterns that result in the intake of undercooked food, disparities in way of life and nutritional habits as well as more direct contact with animals and the surroundings, can enhance this infection.[12–15] Studies in low-resource environments discovered connections between *Campylobacter* infection and poor nutrition as well as intestinal inflammation among children.[16]

Although *C. jejuni* is a bacterial infection commonly associated with gastrointestinal illness, it has emerged as a significant prior infection in the context of Guillain-Barré Syndrome (GBS). The GBS is an immune-mediated condition characterized by flaccid paralysis.[17] Likewise, many studies have suggested an association between an infection with *C. jejuni* and an increased risk of developing Irritable bowel syndrome (IBS). IBS is a chronic gastrointestinal disorder characterized by persistent abdominal pain, bloating, and altered bowel habits.[18] As well, *C. jejuni* may be associated with the development of reactive arthritis, Reiter's syndrome, hemolytic uremic syndrome, and Miller Fisher syndrome.[19,20] This outline the need for preventive measures to reduce the burden of *Campylobacter* infections and their long-term effects on child growth.[21] While data on *Campylobacteriosis* within the Middle East is unfortunately limited, this highlights a disconcerting situation. Notably, the rates of both the infection itself and the resistance to antibiotics used for its treatment are alarmingly high.[22] *Campylobacter* spp has been identified as one of the common bacterial agents associated with diarrheal infections among children in the Middle East.[23,24]

Although data on *Campylobacter* prevalence and antimicrobial susceptibility in Middle Eastern children is still limited, this review aims to grasp available studies to highlight the prevalence, antimicrobial resistance, and associated factors of *campylobacteriosis* in the Children of Middle East.

2. Materials and Methods

This review searched English publications over the past 14 years on *Campylobacter* in children across Middle Eastern countries. Using Google Scholar and PubMed, the key terms "Campylobacter" or "*Campylobacter jejuni*" with "Children", "Infant", "Pediatric", and the name of Middle Eastern Countries were combined with various keywords such as "Prevalence", "Incidence", "Burden", "Epidemiology", "Colonization", and "Diarrhea", "Antibiotic Resistance", "Antimicrobial susceptibility".

Our inclusive criteria included research conducted during the period from 2010 to 2023, prioritizing studies that focus on children or at least 50% of their samples are children or mention the age group prevalence (Figure 1). According to these criteria, the search produced a total of 170 publications related to Campylobacter spp in the Middle Eastern regions. One hundred forty-three were excluded as they either focused on animals, animal products, food, or humans with a children sample size less than 50% or lacked data about children. It is important to note that this article was based on existing research and did not involve any new investigations into human or animal subjects conducted by the authors.

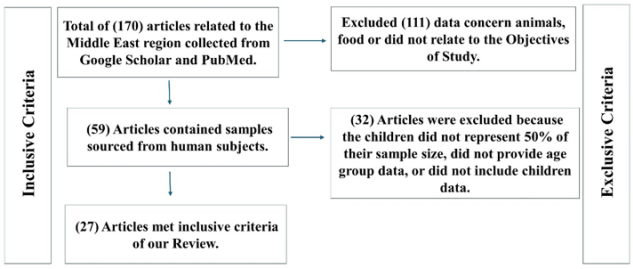

Figure 1: Show the apply of inclusive criteria during screening process

3. Discussion

3.1. Campylobacter jejuni infection in Middle Eastern children with gastroenteritis

The rate of Campylobacteriosis across human populations exhibits substantial variability, being observed in low-income countries at 1.7% to 62.7%. While, in animals, the prevalence of Campylobacter shows considerable variation, ranging from 1.2% to 80%.[1] it has been demonstrated that the rate of Campylobacter among the human population in the Middle East ranges from 1% to 22%.[25,26] A study conducted in Syria has demonstrated a low rate

of campylobacter infection in children. The study also revealed a significant positive association between *C. jejuni* infection and cases of childhood diarrhea.[27] In addition the low prevalence of campylobacter infections also reported in Palestine and Qatar according to the available data.[28,29] While, the moderate rates of campylobacteriosis were listed among children of Jordan,[30] Lebanon,[31,32] Iran,[33–38] Iraq,[39–41] Oman,[42] and Yemen.[43] On other hand, high prevalence rates of pediatric campylobacteriosis reported in Egypt,[10,44,45] Israel,[46] and Turkey.[24] According to the published data, there were discrepancies in the rates of Campylobacter infections among children in the Middle East (Table 1). The fluctuations in the rate are linked to disparities in the detection methods, variations in the age of the targeted population, and additional factors that may enhance infection. Research conducted in both industrialized and developing nations has identified specific risk factors that may cause differences in rate of campylobacteriosis among children, including female gender, shortened natural lactation periods, lower education among younger mothers, and the lack of regular water purification source.[16,47,48] Furthermore, Campylobacter species are reported more frequently in diarrheal cases within many low-and middle-income countries that share similar conditions to those in the Middle East. For example, the prevalence rate of Campylobacter infections in South Asian children ranges from 3.2% to 17.4%, compared to 0% to 13% in non-diarrheal cases.[47] Moreover, recent data from Pakistan documented that 54.6% of diarrheic stool samples from hospitalized children under 5 years old tested positive for *C. jejuni* culture.[49] Likewise, in a low-resource tropical community in Peru, recent data from whole-genome shotgun metagenomic sequencing indicated that over 65% of the acute diarrheal samples of children under 2 years contained co-infections with multiple Campylobacter species within a single stool sample.[50]

It was demonstrated that *C. jejuni* serotype HS4c had the highest occurrence worldwide, accounting for 12.6% of cases. Nevertheless, the primary capsule variations differed depending on the geographic location. In particular regions, serotypes such as HS2, HS3c, HS4c, HS5/31, HS8/17, and HS10 were among the top ten frequently observed.[51] A recent data pointed out that *C. jejuni* CC21 and CC257 clonal complexes were common among children in Iran and HS23/36, HS2, HS4 and HS19 were prominent capsular genotypes of isolates.[33]

While the data on pediatric Campylobacteriosis in the Middle East remains limited (Figure 2), the available information underscores the significance of compylobacteriosis as a prominent health challenge, particularly within low-and-middle-income countries of Middle East. This gap highlights the need for further studies and underscores the public health importance of addressing Campylobacter infections in children, providing a more complete picture of its challenges in this region.

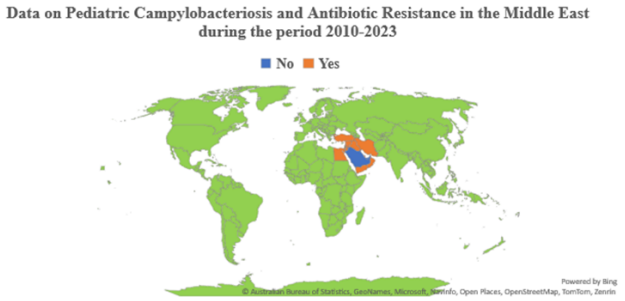

Figure 2: There was no data included in this article from Kuwait, Saudi Arabia, and the United Arab Emirates. While one publication from each of Oman, Lebanon, and Syria, as well as two publications from each of the following countries: Israel, Palestine, Qatar, and Yemen, were included in this review. The remaining publications coming from Egypt, Iran, Iraq, and Turkey.

3.2. Antimicrobial resistance of C jejuni in pediatric papulation in middle East

Antimicrobial resistance of *campylobacter* spp affects both developed and developing nations, this may be related to many factor including introduction of antibiotics in animal husbandry, notably poultry feed.[53,54] There were indications revealed that the resistant *C. jejuni* may not only be present in chicken supplies but also in animals and feral fowls, serving as potential reservoirs and posing a risk for the spread of resistant bacteria.[29,55] In addition, studies in the Middle East regions have demonstrated an increase in the resistance rate of *Campylobacter* spp.[56,57] The presence of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan-drug-resistant (PDR) *Campylobacter* species has also been reported in the Middle East.[44]

There are five primary categories of antibiotics commonly used to treat *campylobacter* infections. These categories include aminoglycosides, beta-lactams, fluoroquinolones, macrolides, and tetracyclines, antibiotics typically reserved for use in severe illness to aid recovery rather than being necessary for every infection.[58] *Campylobacter* species have evolved multiple mechanisms to counter the selective pressure caused by using antibiotics in both veterinary and human medicine. These mechanisms include modifying or mutating the targets of antimicrobial agents, modifying or inactivating antibiotics directly, and reducing the accumulation of drugs as result of drug efflux pumps. These adaptations allow *Campylobacter* to acquire resistance to antibiotics, enabling its survival and proliferation in environments where these drugs are present.[59] It was demonstrated that the presence of imipenem-resistant isolates with metallo-β-lactamase (MBL) genes raises concerns for public health in the

Table 1: Epidemiology of Campylobacter Infection in children of Middle Eastern countries.

Countries	**Period of Study and sample size(Not:** The samples from all studies per country were aggregated as one sample)	***Campylobacter* spp.**	***C. jejuni* (out of total %)**	***C. coli* (out of total %)**	**Referencs**
Egypt	181 samples were collected from children and adult humans from 2011 until 2018.	26-85.7% (PCR)	12.3-71.4%	2.8-14.3%	10,44,45
Jordan	122 blood samples from patients under 19 years.	NA	21.3% (Seroprevalence IgG and IgA)	NA	30
Iran	Samples of stool were obtained from a group of 1902 children who were experiencing diarrhea during the period of 2012 till 2018.	6 - 11.6% (culture) 14.8% (PCR)	19.5% (culture) 33-95% (PCR).	4.8%	33–38
Iraq	A total of 620 cases of diarrhea were recorded among children under the age of 10 during 2017 till 2020	8-17%	75% (PCR)	-	39–41
Israel	843 specimens from Arab Christian as well as Muslim, and Jewish, children collected from January 2003 till December 2012	53.3%	86.7%	4.5%	46
Lebanon	655 fecal samples were gathered from kids during 2016-2018.	12.02- 24.7%	83.2%	19.9%	31,32
Oman	790 fecal specimens were gathered from different aged patients who suffered from gastroenteritis during the period of 2019	-	10.2%	-	42
Palestine	132 diarrhea samples from all age patients (75% under 5 years) in 2010	2.2%	-	-	28
Qatar	Fecal samples collected from different age groups patients who suffered from for the period 23-2013	1.73–2.06%	-	-	29
Turkey	8528 Stool Samples were collected for different ages groups during 2010 to 2016	71% in Children. 52.2% in age group 0-5 years (PCR) & 21.7% in cohort of 6-14years (PCR).	NA	NA	24,52
Syria	73 fecal specimens had been obtained from diarrheic children under 14 at two local hospitals between September and December 2017.	6.84%	4.10%	2.73%	27
Yemen	A total of two hundred fecal samples from children under the age of twelve were acquired at General Thamar Hospital and private laboratories within the timeframe spanning from February to November in the year 2011.	13.50%	70.4%	22.22%	43

third world.[49] Furthermore, *Campylobacter* shows high Tetracycline and Ciprofloxacin resistance via CmeABC efflux pumps and acquired resistance genes like tetO and gyrA. These multiple, simultaneous mechanisms demonstrate the organism's advanced strategies to develop high antibiotic tolerance, overcoming diverse antimicrobial classes.[60,61] Moreover, the genetic elements of *Campylobacter* that harbor clusters of genes conferring resistance to aminoglycosides and macrolides were discovered. These discrete genetic elements concentrate various resistance determinants against these two antibiotic classes in one location. It enables *Campylobacter* to readily develop cross-resistance against these important antibiotic categories.[59]

A recent investigation carried out in Egypt on 120 isolates of *C. jejuni* and *C. coli* sourced from human samples and chickens pointed out that 75% of isolates were MDR, 20.8% were XDR, and 4.2% were PDR isolates.[44] The complete resistance against Ampicillin in *C. jejuni* was reported in Egypt, Iraq, and Yemen.[41,44,62] Meanwhile, it was demonstrated that 40.3% of isolates in one Turkish study had Ampicillin non-susceptibility.[52] On other hand approximately a quarter of isolated strains, exhibited a resistant capacity for Ampicillin in studies conducted in Lebanon,[31] and Iran.[35] High Ciprofloxacin resistance rates were documented in research data from Israel,[63] Egypt,[44] Oman,[42] Turkey,[52] and Iran.[35] Unfortunately, *C. jejuni* showed completed non-susceptibility for Erythromycin in Egypt,[44] as well as a high resistant rates were reported in Iraq and Palestine.[40,42] In contrast moderate rate of resistance against Erythromycin was found in Iran.[35] While low Erythromycin non-susceptibility rate was documented in other regions of Middle East (Table 2). As well a high Gentamycin resistance was illustrated in Egypt,[44] in compare with low rate or no updated data in other countries. Complete Tetracycline non-susceptibility was listed in Egypt[44] and Iraq,[41] whereas high resistant rate was indicated in Israel, Iran, and Oman.[35,42,63] The resistant prevalence of *C. jejuni* against Trimethoprim Sulfamethoxazole was found at 100% in one investigation form Egypt.[44] At the same time the high resistance of Trimethoprim Sulfamethoxazole was demonstrated in publications from Iraq and Turkey.[40,52]

Although there is scant data about *Campylobacter* species isolated from children in the Middle East, multiple resistant strains of *Campylobacter* from human sources have been documented in many recent publications from the Middle East regions.[57,64,65] The observed resistance patterns in *Campylobacter* in the Middle East may be linked to several factors, with self-medication and antimicrobial abuse remaining a significant contributing factor that create such issue.[66–68] This circumstance poses a significant challenge in the treatment of *Campylobacter* infections as some strains have become resistant to multiple antibiotics, limiting the effectiveness of available treatment options. Therefore, utilizing antibiotic sensitivity testing can help guide the selection of the most effective antibiotic for treatment. This approach ensures that the chosen antibiotic is tailored to the specific strain of *Campylobacter*, optimizing the chances of successful treatment, and minimizing the development of antibiotic resistance.[69] However, it is important to observe that the occurrence of multi-drug resistance among microbes is widespread and has notable implications particularly in nations with lower economic resources and middle-income status.[70]

3.3. Current challenges of campylobacter infections among middle eastern children

The access to public health interventions and healthcare is significantly limited in some regions of Middle East.[71] Furthermore, the prevalence of diarrhea among children aged less than 5 years was high, especially in politically instable countries like Yemen where 29.07% of children were suffered from acute diarrhea. The highest rates were observed among those who were under 12 months old.[72] The incidence of diarrhea among children under the age of five in Yemen was 7.0 (5.5-8.9) episodes per person-year.[73] Unfortunately, this challenges is compounded by self-medication that remains a common behavior in many regions of the Middle East.[66–68] Similarly, in some regions of the Middle East, physicians feel highly pressured to administer broad-spectrum antibiotics due to the unavailability of antimicrobial susceptibility tests that guide antibiotic choices for prescriptions.[74] In addition, the diet significantly impacts *C. jejun*i infection, influencing micronutrient availability, microbiome composition, and triggering a lasting immune response in children exposed early. However, short-term consequences include poor nutrient absorption, oral vaccine failure, impaired cognitive function, and increased mortality rates in children under five.[75] Likewise, high antibiotic resistance rates have been reported in *Campylobacter* isolates collected from human, animals, animal products, and food sources across various regions of the Middle East.[2,14,26,76,77] Furthermore, many virulence genes have been demonstrated in *Campylobacter* isolates gathered from humans and other sources in the regions of the Middle East.[77] This complex situation poses significant challenges for the children of the Middle East and needs urgent interventions.

4. Conclusion

The limited availability of data on *Campylobacter* infections in Middle Eastern children, coupled with high rates of *campylobacteriosis*, potent virulence factors in regional *Campylobacter* isolates, high antimicrobial resistance, and political instability in areas such as Iraq, Syria, and Yemen pose significant challenges for children in the region. To

Table 2: Antimicrobial resistance of *C. jejuni* in children of middle east

Countries	Study Period	Antimicrobial agents						
		AMP	CIP	E	GN	TE	STX	
Egypt	2017-2018	100%	84%	100%	92%	100%	100%	44
Lebanon	2016-2017	30.8%	17.8%	4.1%	NA	22.9%	NA	31
Iran	2015	28.8%	0-71.1%	33.6-68.8%	8.8-50%	17-82.2%	NA	35,37
Iraq	2019-2020	100%	26.9%	91.6%	34.6-50%	100	91.6%	40,41
Israel	2015-2021	NA	95%	0.5%	2.1%	93%	NA	63
Oman	2019	NA	26.9-80%	0	NA	80%	NA	42
Palestine	2010	NA	33.3%	75%	NA	NA	NA	28
Qatar	2005 -2012	NA	63.2%	8.6%	0	0	0	28
Turkey	2010-2011	40.3%	74.3%	5.9- 6.3%	NA	25%	92.6%	52,61
Yemen	2012-2013	100%	46.2	NA	38%	34.7%	NA	62

Ampicillin (AMP), Ceftriaxone (CTX), Ciprofloxacin (CIP), Erythromycin (E), Gentamycin (GN), Tetracycline (TE), Sulphathiazole/Trimethoprim (SXT), and non-available (NA).

overcome these challenges, it is necessary to implement targeted interventions, enhance healthcare accessibility, adopt appropriate antibiotic prescription practices, and apply infection control measures in this specific population and a need for research to shed light on this obscure topic that has not been adequately addressed in children of this setting of the world.

5. Source of Funding

None.

6. Conflict of Interest

Authors report no conflicts of interest.

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