The Status of antimicrobial resistance in *Campylobacter* spp. isolated from animals and humans in Southeast Asia: a review

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**Abstract**

*Campylobacter* is considered to be a major foodborne pathogen associated with human bacterial gastroenteritis in many parts of the world. Southeast Asia (SEA) has been challenging for infectious diseases and antimicrobial resistance in recent years. Antibiotic resistance in *Campylobacter* isolates has been reported in humans and animals in this region. Since the SEA region is one of the top tourist destinations of the world, the provision of safe food is of importance for the travel-related foodborne infections. Therefore, it is essential to elucidate the status of antibiotic resistance of *Campylobacter* spp. in the SEA region to reduce the impact of infection and to implement mitigation strategies. This review provides further insights into the true burden of the trend of antimicrobial resistance in *Campylobacter* spp. in the SEA region. Based on the published data, antimicrobial resistance of both human and animal in *Campylobacter* isolates is becoming increasingly common in SEA, especially to fluoroquinolones and tetracycline. Therefore, appropriate interventions are required to minimize *Campylobacter* contamination and to harmonize the monitoring of antimicrobial resistance in SEA.

**Keywords:** animal, antimicrobial resistance, *Campylobacter*, human, public health, Southeast Asia

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Received January 18, 2020.
Accepted September 29, 2020.
Introduction

Thermophilic Campylobacter is a major bacterial pathogen that causes foodborne infections around the world, especially in the SEA region. Campylobacter is also an important leading cause of diarrheal disease in SEA (Mason et al., 2017). In Singapore, an increasing trend of Campylobacter infection was reported in human isolates from 1990 to 2015. A higher prevalence of Campylobacter infection was detected in post-travel stool samples of Finnish travelers to SEA than those who traveled to other parts of the world in recent years (Laaveri et al., 2018). Antimicrobial resistance associated with Campylobacter infection is an emerging problem worldwide. Antimicrobial resistance in Campylobacter from both human and animal isolates has become increasingly common in SEA countries (Premarathe et al., 2017). Since the SEA region is one of the top tourist attractions of the world, Campylobacter-associated traveler’s diarrhea and the emergence of antimicrobial resistance have become public health concerns in this region.

Early studies in the SEA region showed a high resistance rate to erythromycin (ERY) among Campylobacter isolates from human sources in Thailand (65%) and Singapore (90%) (Lim and Tay, 1992; Taylor et al., 1987). Consistently, a high resistance rate to ERY (98%) has been observed in Campylobacter isolated from poultry products in the Philippines in recent years (Lim et al., 2017). The increasing resistance rate of Campylobacter to ERY is alarming in the SEA region since the resistance rate to ERY is generally low in other parts of the world. A major increase in the incidence of fluoroquinolone (FQ) resistance in Campylobacter has also been reported in SEA, for example, in Thailand the rate of FQ resistance in human isolates increased from zero before 1991 to 84% in 1995 (Hoge et al., 1998). Newer studies have reported even higher rates of FQ resistance in Campylobacter among human isolates (95%) in Thailand and poultry isolates (88%) in Vietnam (Mason et al., 2017; Pham et al., 2016). In SEA, high tetracycline (TET) resistance in Campylobacter among humans (82%) and animal (77%) isolates have also been observed (Premarathe et al., 2017; Serichantalergs et al., 2010).

Keeping the above facts in view, it is important to understand the status of antimicrobial resistance in Campylobacter isolates and especially the contribution of humans and animals in the SEA region in order to reduce the burden of infection and to implement safety strategies. In this review, we summarize the status of antibiotic resistance in Campylobacter from human and animal sources with a special emphasis on resistance to FQ, macrolides and TET in the SEA region.

The status of antimicrobial resistance in Campylobacter spp. among SEA human isolates: Campylobacter which is a major cause of gastroenteritis in children, travelers and military personnel deployed in developing countries have increasingly become resistant to the antimicrobials used to treat diarrhea. Mason et al., (2017) has reported significant morbidity concerning FQ resistance associated with Campylobacter infections in Thailand.


Antibiotic resistance of Campylobacter isolated from human sources (children less than 5 years of age and US military soldiers) showed resistance to FQ (77 and 7 %) and azithromycin (AZM, 6 and 0 %), respectively in Vietnam and Thailand from 1996 to 1999 (Isenbarger et al., 2002). Co-resistance between FQ and AZM was also observed in Thailand in that study. In 1998, a study on Campylobacter isolates from local people and travelers in Thailand for up to 15 years showed an increasing resistance trend to FQ from 0 to 84% and AZM up to 15% as determined by the disk diffusion method (Hoge et al., 1998) Hoge et al., (1998) also reported that due to the increasing resistance trend of Campylobacter, newer classes of antibiotics, as well as alternative strategies such as an enteric vaccine, should be amended to treat diarrheal disease.

Campylobacter isolates collected from travelers returning to Finland showed an increasing resistance trend to FQ from 60 to 77 % from 1995 to 2000 (Hakanen et al., 2003). An increasing FQ resistance trend of Campylobacter was also reported among travelers and US military personnel who were deployed to Thailand from 1998 to 2003, in which, almost 95% of isolates were reported resistant to FQ but 99 % were susceptible to macrolides (AZM and ERY) (Serichantalergs et al., 2010). Likewise, 96% of Campylobacter isolates from human sources were resistant to FQ with no resistance to AZM as reported in Thailand (Sanders et al., 2002). Consistent with the studies in SEA, Engberg et al., (2001) reported an increasing FQ resistance in Campylobacter spp. among human isolates worldwide (Engberg et al., 2001). A minimized use of FQ in food-producing animals was recommended to preserve antibiotic sensitivity to Campylobacter.

In 2006, a study of the antimicrobial resistance of Campylobacter in children hospitalized with diarrhea and healthy farm workers in northern Thailand showed high resistance to FQ and TET but no resistance to gentamicin (GEN) (Padungtrod et al., 2006). Padungtrod et al., (2006) mentioned antimicrobial use in both humans and animals as the most important factor for the development of bacteria with increased resistance. Accordingly, in a study, FQ resistance in Campylobacter was seen to have exceeded 85% in Thailand (Tribble et al., 2007). Less efficacy of FQ as compared to macrolides (AZM) was also reported for the treatment of acute diarrhea. Surprisingly, FQ was effective against most bacterial enteropathogens in children younger than 5 old with only 27% of resistance among Campylobacter isolates as determined by the disk diffusion technique in Vietnam (Bodhidatta et al., 2007). However, Campylobacter isolates from Thai children with diarrhea showed 67% and 12.5% resistance rates to FQ and macrolides, respectively (Pham et al., 2016). In Thailand, high rates of antimicrobial resistance to FQ (96%) and TET (57%) were reported but a lower resistance rate was reported to ERY (14%) in humans with diarrhea as determined by the agar dilution technique (Boonmar et al., 2007).

In Cambodia (2011), 50% of Campylobacter isolates from inpatient and outpatient children with diarrhea, showed resistance to FQ (from 40 to 80 %) and ERY (from 3 to 8 %) in international
travelers who traveled to SEA from 1994 to 2006 (Vlieghé et al., 2008). In 2017, an increasing resistance trend was reported related to traveler’s diarrhea as well as FQ resistance expansion from Campylobacter in SEA since the 1990s (Tribble, 2017). Accordingly, 68% and 56% of the resistance rate to FQ and TET was reported among Campylobacter isolates from international travelers to the SEA region between 2007 and 2014 (Post et al., 2017).

Early studies reported an increasing resistance trend to ERY in Campylobacter isolates from human sources in Thailand (65%) and Singapore (90%) (Lim and Tay, 1992; Tayloor et al., 1987). Although macrolides have shown an increasing resistance trend among human isolates in recent years (Pham et al., 2016), however, in the most recent study, the rate of ERY resistance to Campylobacter was as low as 4% for international travelers to the SEA region during 2007 to 2014 (Post et al., 2017). Furthermore, macrolides (e.g. AZM) are known to be much more effective than FQ in the excretion of Campylobacter species (Kuschnier et al., 1995). Multidrug resistance (MDR) which is defined as the resistance to three or more antimicrobial classes is increasing worldwide (Murray and Blath, 2017). In SEA, most of Campylobacter isolates from travelers and US military personnel with diarrhea were MDR in Thailand from 1998 to 2003 (Serichantalergs et al., 2010). Consistently, in 2010, most of the human Campylobacter isolates were reported as MDR to different classes of antibiotics in Thailand (Serichantalergs et al., 2010).

The status of Antimicrobial resistance in Campylobacter spp. among SEA animal isolates: Antimicrobial resistance in both human and animal Campylobacter isolates has become increasingly common in SEA (Nhung et al., 2016). There is a great similarity between antimicrobial used in animal production and human medicine, and therefore resistance against antimicrobials is of great importance for human medicine (Tang et al., 2017).

In 2006, the prevalence of Campylobacter with antimicrobial resistance in chickens, pigs, and dairy cows was studied in Thailand (Padungtod et al., 2006). The results showed significant differences in the rate of resistance in Campylobacter among animal isolates at the farm level with a high rate of resistance to FQ and TET and low resistance rate to GEN (5%) in all the study populations. In addition, meat isolates collected at the market had a higher resistance rate compared with isolates collected from animals on the farm or at the slaughterhouse (Padungtod et al., 2006). In 2008, high resistance rates to FQ (90%) and lower resistance levels to ERY (29%) were reported among Campylobacter isolates from chicken meat in northeastern Thailand (Noppon et al., 2011). In 2009, minor resistance rates to FQ (31%) and AZM (7%) were reported in Campylobacter isolates from chickens in two provinces (Mahasarakam and Khon Kaen) in Thailand as determined by the E-test method (Noppon et al., 2009). In Vietnam (2010), 71% of Campylobacter isolates from chickens were resistant to FQ and TET with only a 7% resistance rate to ERY and GEN (Schwan, 2010). Similarly, a high rate (70%) of FQ resistance in Campylobacter isolates from poultry was reported at the retail market in Cambodia (Lay et al., 2011). A low resistance rate was also observed for AZM (1%), ERY (2%), and GEN (0%) in the mentioned study.

In Thailand (2013), antimicrobial resistance rates among Campylobacter isolates in chicken at slaughter were 81%, 41%, 31%, 9% and 0% for ciprofloxacin (CIP), TET, AMP, ERY and GEN, respectively (Chokboonmongkol et al., 2013). The most common combination of MDR was reported for AMP, TET and CIP. On-farm biosecurity measures followed by control measures at the slaughterhouse were suggested to reduce cross-contamination of Campylobacter. Another study in Thailand reported the most common resistance pattern in Campylobacter isolates were MDR to FQ, TET and TMP (trimethoprim) (Thomrongsuwannakij et al., 2017). Consistent with the studies in Thailand, the most common resistance rate was observed for AMP (77%), followed by CIP (70%), TET (55%), ERY (20%) and GEN (11%) in Campylobacter isolates from chicken meat in the Philippines (Sison et al., 2014). In 2015, 35% of the Campylobacter isolates from chicken were reported as MDR in Thailand with the most common resistance pattern being for CIP (96%), TET (84%) and AMP (35%) (Charanuntakorn et al., 2015). However, less than 1% of ERY-resistant and no GEN-resistant Campylobacter were observed in that study.

Contrary to the study in the Philippines, high resistance rates to ERY (98.6%) and GEN (65.2%) were observed in Campylobacter isolates from poultry products in wet markets and supermarkets in the Philippines (2016) as determined by broth microdilution assay (Lim et al., 2017). In Vietnam (2016), the antibiotic resistance in Campylobacter isolates from chicken and pig meat showed no resistance to GEN but high resistance rates to FQ (78%) and TET (78%) were reported (Nguyen et al., 2017). In Malaysia (2017), low resistance rates were observed for FQ (34%), ERY (31%) and GEN (15%) in Campylobacter isolates from beef as determined by the disk diffusion method (Premarathne et al., 2017). Different from the study in Malaysia, 98% of Campylobacter spp. isolates from the broiler production chain were resistant to FQ in Thailand in 2017 (Thomrongsuwannakij et al., 2017).

A high rate of antibiotic resistance to FQ (80%), ampicillin (AMP, 81%) and TET (96%) and low resistance rate to GEN (5%) and ERY (1%) was reported in Campylobacter isolated from ducks in Malaysia as determined by the disk diffusion method (Adzitye et al., 2012). Also, a study in Thailand reported that almost 55% of Campylobacter isolated from ducks were resistant to FQ, while none of the isolates were resistant to ERY and GEN as determined by the broth microdilution method (Saengthongpinit et al., 2015).

In conclusion, this review highlighted a large variation in data available for phenotypic antimicrobial resistance testing in SEA. Except for some countries in the SEA region (e.g. Thailand) that are monitoring antimicrobial resistance in foodborne pathogens coherently, there is a scarcity of data for other countries in the SEA region. Furthermore, the different results reported in terms of the prevalence of antimicrobial resistance in Campylobacter isolates is probably due to the variety of methods used, therefore,
it would be desirable to move towards the harmonization of surveillance systems to monitor antimicrobial resistance in animal production, as well as the testing of animal products for antimicrobial residues in foods of animal origin. Of particular urgency is the implementation of policies that restrict the use of certain antimicrobials in animal production. It is hoped that all SEA countries implement policies that restrict the use of certain antimicrobials in animal production. In the meantime, the trend of antimicrobial resistance of Campylobacter spp. in the SEA region must be further investigated.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Reference</th>
<th>Sample</th>
<th>Species</th>
<th>Resistance rates</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>2011</td>
<td>Meng et al. (2011)</td>
<td>Inpatient and outpatient children (Stool)</td>
<td>C. jejuni, C. coli</td>
<td>C. jejuni (FQ, 32%; macrolides, 2%; aminoglycosides, 0%; AMP, 14%; TET, 27%). C. coli (FQ, 57%; macrolides, 9%; aminoglycosides, 17%; AMP, 22%; TET, 44%).</td>
<td>Low resistance rates to aminoglycosides and macrolides in Cambodia.</td>
</tr>
<tr>
<td>SEA</td>
<td>2017</td>
<td>Post et al. (2017)</td>
<td>International a traveller to SEA (stool)</td>
<td>Campylobacter spp.</td>
<td>CIP (68%), ERY (4%), TET (56%)</td>
<td>Southern Asia had higher ERY resistance as compared to other regions.</td>
</tr>
<tr>
<td>Thailand</td>
<td>1987</td>
<td>Taylor et al. (1987)</td>
<td>Up to 5-years old (stool)</td>
<td>C. jejuni, C. coli</td>
<td>ERY (C. jejuni 53%, C. coli 91%) from Orphanage-acquired isolates; ERY (C. jejuni 11%, C. coli 46%) from community-acquired strains:</td>
<td>Lack of efficacy of ERY for treatment of diarrheal illnesses.</td>
</tr>
<tr>
<td>Thailand</td>
<td>1995</td>
<td>Kuschner et al. (1995)</td>
<td>Travelers to Thailand (stool)</td>
<td>Campylobacter spp.</td>
<td>AZM, 0%; CIP, 50%</td>
<td>AZM therapy may be an effective alternative to CIP therapy.</td>
</tr>
<tr>
<td>Thailand</td>
<td>2002</td>
<td>Sanders et al. (2002)</td>
<td>Military personnel (stool)</td>
<td>Campylobacter spp.</td>
<td>CIP, 96%.</td>
<td>Therapy with FQ for traveler’s diarrhea may be ineffective due to the high resistance rate.</td>
</tr>
<tr>
<td>Thailand</td>
<td>2006</td>
<td>Padungtod et al. (2006)</td>
<td>Healthy and hospitalized adults</td>
<td>Campylobacter spp.</td>
<td>Healthy (CIP, 20%; ERY, 33%; GEN, 0%, NAL, 60%; TET, 40%). Hospitalized (CIP, 69%; ERY, 78%; GEN, not tested; NAL, 65%; TET, 34%).</td>
<td>Antimicrobial use in humans as the most important factor for the development of antimicrobial resistance.</td>
</tr>
</tbody>
</table>
Thailand 2010 Serichantagergs et al. (2010) Travelers and military personnel C. jejuni AMP, 28.9%; CIP, 93%; KAN, 5.9%; NAL, 95%; NOR, 2%; STR, 0.7%; SXT, 57.9%; TET, 81.9. C. jejuni isolates from Thailand had high MDR rate.

Thailand 2016 Pham et al. (2016) children with diarrhea (stool) Campylobacter spp. CIP (67%), macrolides (12.5%) Continuous monitoring of Campylobacter resistance to FQ and macrolides in Thailand.

Thailand 2017 Mason et al. (2017) Military personnel (stool) C. jejuni, C. coli Campylobacter spp. (MDR, 95%), C. jejuni (AMP, 34%; AZM, 0%; CIP, 89%; NAL, 94%; TET, 68%), C. coli (AMP, 20%; AZM, 10%; CIP, 90%; NAL, 100%; TET, 70%). High FQ resistance with Campylobacter infections in Thailand.

Thailand 2010 Serichantagergs et al. (2010) Travelers and military personnel C. jejuni AMP, 28.9%; CIP, 93%; KAN, 5.9%; NAL, 95%; NOR, 2%; STR, 0.7%; SXT, 57.9%; TET, 81.9. C. jejuni isolates from Thailand had high MDR rate.

Thailand 2016 Pham et al. (2016) children with diarrhea (stool) Campylobacter spp. CIP (67%), macrolides (12.5%) Continuous monitoring of Campylobacter resistance to FQ and macrolides in Thailand.

Thailand 2017 Mason et al. (2017) Military personnel (stool) C. jejuni, C. coli Campylobacter spp. (MDR, 95%), C. jejuni (AMP, 34%; AZM, 0%; CIP, 89%; NAL, 94%; TET, 68%), C. coli (AMP, 20%; AZM, 10%; CIP, 90%; NAL, 100%; TET, 70%). High FQ resistance with Campylobacter infections in Thailand.

Thailand 2010 Serichantagergs et al. (2010) Travelers and military personnel C. jejuni AMP, 28.9%; CIP, 93%; KAN, 5.9%; NAL, 95%; NOR, 2%; STR, 0.7%; SXT, 57.9%; TET, 81.9. C. jejuni isolates from Thailand had high MDR rate.

Table 2: Antimicrobial resistance in Campylobacter spp. among SEA animal isolates

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Reference</th>
<th>Sample</th>
<th>Species</th>
<th>¹Resistance rates</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>2011</td>
<td>Lay et al. (2011)</td>
<td>Poultry (neck skin)</td>
<td>C. jejuni, C. coli</td>
<td>C. jejuni (CIP, 20.3%; ERY, 2.9%; GEN, 0%; NAL, 69.5%), C. coli (CIP, 7.5%; ERY, 0%; GEN, 2.5%; NAL, 15%)</td>
<td>High antibiotic resistance rate among Campylobacter spp. isolates from retail poultry in Cambodia.</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2012</td>
<td>Adzitey et al. (2012)</td>
<td>Duck (carcases)</td>
<td>C. jejuni</td>
<td>AMP, 81%; CIP, 76%; GEN, 5%; ERY, 1%; NAL, 84%; TET, 96%</td>
<td>C. jejuni from ducks were resistant to most of the antibiotics tested.</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2017</td>
<td>Premarathne et al. (2017)</td>
<td>Cattle (beef)</td>
<td>Campylobacter spp.</td>
<td>AMP, 69%; CIP, 15%; ERY, 31%; NAL, 54%; TET, 77%</td>
<td>A high percentage of Campylobacter spp. was resistant to TET and AMP.</td>
</tr>
<tr>
<td>Philippines</td>
<td>2014</td>
<td>Sison et al. (2014)</td>
<td>Chicken (meat)</td>
<td>Campylobacter spp.</td>
<td>AMP, 77.3%; CIP, 70.4%; ERY, 20.2%; GEN, 11.4%; TET, 54.6%</td>
<td>The most common combination of MDR (34%) was to AMP, CIP, and TET.</td>
</tr>
<tr>
<td>Philippines</td>
<td>2016</td>
<td>Lim et al. (2016)</td>
<td>Chicken (meat)</td>
<td>Campylobacter spp.</td>
<td>ERY, 98.6%; GEN, 65.2%; NAL, 98.1%; TET, 94.2%</td>
<td>The high rate of resistance of Campylobacter to ERY, NAL, and TET in Manila.</td>
</tr>
<tr>
<td>Country</td>
<td>Year</td>
<td>Authors</td>
<td>Animal/Environment</td>
<td>Organism</td>
<td>Resistance to Antimicrobials</td>
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<tr>
<td>Thailand</td>
<td>2006</td>
<td>Padungtod et al.</td>
<td>Chicken, pigs, dairy cows</td>
<td>Campylobacter spp.</td>
<td>Chicken (AMP, 0%; CIP, 54%; ERY, 6%; GEN, 0%; NAL, 60%; TET, 53%), Pig (AMP, 0%; CIP, 78%; ERY, 83%; GEN, 0%, NAL, 84%, TET, 87%), Dairy cow (AMP, 17%; CIP, 29%; ERY, 6%; GEN, 0%, NAL, 12%, TET, 12%). Pig showed higher rates of resistance of Campylobacter to FQ, ERY and TET as compared to chicken and dairy cow isolates.</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>2008</td>
<td>Noppon et al.</td>
<td>Chicken (meat)</td>
<td>C. jejuni</td>
<td>CHL, 13%; DOX, 37%; ERY, 29%; OFX, 91%; High resistant rate to OFX. More cautious use of OFX and DOX.</td>
<td></td>
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<tr>
<td>Thailand</td>
<td>2009</td>
<td>Noppon et al.</td>
<td>Chicken (faeces)</td>
<td>Campylobacter spp.</td>
<td>AZM, 6.40%; CIP, 30.37%; CAZ, 0%; CHL, 0%, DOX, 12.65%; Resistance to antimicrobials would increase with the increasing age of birds.</td>
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<tr>
<td>Thailand</td>
<td>2013</td>
<td>Chokboonmongkol et al.</td>
<td>Broiler (caeca and skin)</td>
<td>Campylobacter spp.</td>
<td>AMP, 31.20%; CIP, 81.2%; ERY, 9.4%; GEN, 0%; TET, 40.6%; The most common combination of MDR was to CIP, TET and AMP.</td>
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<tr>
<td>Thailand</td>
<td>2015</td>
<td>Charununthornkorn et al.</td>
<td>Broiler (cloacal swab)</td>
<td>C. jejuni</td>
<td>AMP, 34.78%; CIP, 95.65%; ERY, 0.69%; GEN, 0%; TET, 84.06%; Routine monitoring of antimicrobial resistance of Campylobacter in contracted broiler farms.</td>
<td></td>
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<tr>
<td>Thailand</td>
<td>2015</td>
<td>Saengthongpinit et al.</td>
<td>Duck (cloacal swab)</td>
<td>Campylobacter spp.</td>
<td>CIP, 54%; GEN, 0%, NAL, 58%; TET, 12.5%; The excessive use of antimicrobial agents in laying ducks results in poor response to FQ in patients infected with Campylobacter.</td>
<td></td>
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<tr>
<td>Thailand</td>
<td>2017</td>
<td>Thomrongsubannakij et al.</td>
<td>Chicken (cloacal swabs)</td>
<td>C. jejuni, C. coli</td>
<td>C. jejuni (SXT, 81.9%, TET, 97.9%); C. coli (SXT, 36%, TET, 55%); High level of MDR and high resistance rates to antimicrobials.</td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>2010</td>
<td>Schwan (2010)</td>
<td>Chicken</td>
<td>Campylobacter spp.</td>
<td>CIP, 64%; ERY, 0%, GEN, 9%; NAL, 64%, TET, 68%; Treatment of diarrhea with FQ and TET will be ineffective compared to the treatment with aminoglycosides or macrolides.</td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>2016</td>
<td>Nguyen et al.</td>
<td>Chicken meat and pork</td>
<td>C. jejuni</td>
<td>CIP, 66.7%; ERY, 25%; GEN, 0%; NAL, 87%; TET, 75%; Low resistance rate to ERY and GEN.</td>
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</tbody>
</table>

Acknowledgements

This work is supported by Ratchadapisek Somphot Fund for Postdoctoral Fellowship, Chulalongkorn University.

References


