

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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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 (Premarathne *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 (93%) 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 (Premarathne *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) (Padungtod *et al.*, 2006). Padungtod *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 (Meng *et al.*, 2011). An increasing resistance trend was reported for FQ (from 40 to 80 %) and ERY (from 3 to 8 %) in international

travelers who traveled to SEA from 1994 to 2006 (Vlieghe *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; Tayylor *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 (Kuschner *et al.*, 1995).

Multidrug resistance (MDR) which is defined as the resistance to three or more antimicrobial classes is increasing worldwide (Murray and Blyth, 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 (Maharakam 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 level 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%) (Charunontakorn *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 (Adzitey *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 antimicrobials of critical importance. 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 1 Antimicrobial resistance in *Campylobacter* spp. among SEA human isolates

Country ¹	Year	Reference	Sample	Species ²	Resistance rates ³	Conclusion
Cambodia	2011	Meng et al. (2011)	Inpatient and outpatient children (Stool)	<i>C. jejuni</i> , <i>C. coli</i>	<i>C. jejuni</i> (FQ, 32%; macrolides, 2%; aminoglycosides, 0%; AMP, 14%; TET, 27%). <i>C. coli</i> (FQ, 57%; macrolides, 9%; aminoglycosides, 17%; AMP, 22%; TET, 44%).	Low resistance rates to aminoglycosides and macrolides in Cambodia.
Singapore	1992	Lim and Tay (1992)	Children 5-years old (stool)	<i>Campylobacter</i> spp.	ERY, 89%.	High resistance rate to ERY in Singapore.
SEA	2003	Hakanen et al. (2003)	International travelers to SEA (stool)	<i>C. jejuni</i>	1995–1997 (FQ, 60%), 1998–2000 (FQ, 77%)	Significant increase in FQ resistance among <i>C. jejuni</i> travelers' isolates.
SEA	2017	Post et al. (2017)	International a traveller to SEA (stool)	<i>Campylobacter</i> spp.	CIP (68%), ERY (4%), TET (56%)	Southern Asia had higher ERY resistance as compared to other regions.
Thailand	1987	Taylor et al. (1987)	Up to 5-years old (stool)	<i>C. jejuni</i> , <i>C. coli</i>	ERY (<i>C. jejuni</i> 53%, <i>C. coli</i> 91%) from Orphanage-acquired isolates; ERY (<i>C. jejuni</i> 11%, <i>C. coli</i> 46%) from community-acquired strains:	Lack of efficacy of ERY for treatment of diarrheal illnesses.
Thailand	1995	Kuschner et al. (1995)	Travelers to Thailand (stool)	<i>Campylobacter</i> spp.	AZM, 0%; CIP, 50%	AZM therapy may be an effective alternative to CIP therapy.
Thailand	1998	Hoge et al. (1998)	Indigenous persons and travelers	<i>Campylobacter</i> spp.	From 1991-1995 (CIP, 0-84%), From 1994-1995 (AZM, 7-15%).	Enteric pathogens in Thailand have developed resistance to FQ.
Thailand	2002	Sanders et al. (2002)	Military personnel (stool)	<i>Campylobacter</i> spp.	CIP, 96%.	Therapy with FQ for traveler's diarrhea may be ineffective due to the high resistance rate.
Thailand	2006	Padungtod et al. (2006)	Healthy and hospitalized adults	<i>Campylobacter</i> spp.	Healthy (CIP, 20%; ERY, 33%; GEN, 0%, NAL, 60%; TET, 40%), Hospitalized (CIP, 69%; ERY, 78%; GEN, not tested; NAL, 65%; TET, 34%).	Antimicrobial use in humans as the most important factor for the development of antimicrobial resistance.
Thailand	2007	Boonmar et al. (2007)	Hospitalized patient (feces)	<i>C. jejuni</i>	AMP, 29%; CIP, 96%; ERY, 14%; NAL, 96%; TET, 57%.	High resistance to FQ among <i>C. jejuni</i> isolated from patients in Thailand.

Thailand	2010	Serichantalergs et al. (2010)	Travelers and military personnel	<i>C. jejuni</i>	AMP, 28.9%; CIP, 93%; KAN, 5.9%; NAL, 95%; NOR, 2%; STR, 0.7%; SXT, 57.9%; TET, 81.9%.	<i>C. jejuni</i> isolates from Thailand had high MDR rate.
Thailand	2016	Pham et al. (2016)	children with diarrhea (stool)	<i>Campylobacter</i> spp.	CIP (67%), macrolides (12.5%)	Continuous monitoring of <i>Campylobacter</i> resistance to FQ and macrolides in Thailand.
Thailand	2017	Mason et al. (2017)	Military personnel (stool)	<i>C. jejuni</i> , <i>C. coli</i>	<i>Campylobacter</i> spp. (MDR, 95%), <i>C. jejuni</i> (AMP, 34%; AZM, 0%; CIP, 89%; NAL, 94%; TET, 68%), <i>C. coli</i> (AMP, 20%; AZM, 10%; CIP, 90%; NAL, 100%; TET, 70%).	High FQ resistance with <i>Campylobacter</i> infections in Thailand.
Thai-Viet	2002	Isenbarger et al. (2002)	Children and US soldiers (stool)	<i>Campylobacter</i> spp.	Thailand (AZM, 6%; FQ, 77%); Vietnam (AZM, 0%; FQ, 7%).	Resistance to FQ correlated with resistance to AZM in <i>Campylobacter</i> in Thailand.
Vietnam	2007	Bodhidatta et al. (2007)	3-5 years old (stool)	<i>Campylobacter</i> spp.	Overall: 27%, AMP, 9%; AZM, 0%; CIP, 27%; NAL, 36%; SXT, 64%.	FQ was effective against <i>Campylobacter</i> .

¹SEA: Southeast Asia, Thai-Viet: Thailand-Vietnam.

²*C. jejuni* (*Campylobacter jejuni*), *C. coli* (*Campylobacter coli*).

³Resistance rate to AZM (azithromycin), CIP (ciprofloxacin), ERY (erythromycin), FQ (fluoroquinolone), GEN (gentamicin), NAL (nalidixic acid), MDR (multi-drug resistance), NOR (norfloxacin), STR (streptomycin), SXT (Trimethoprim/sulfamethoxazole), TET (tetracycline).

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

Country	Year	Reference	Sample	¹ Species	² Resistance rates	Conclusion
Cambodia	2011	Lay et al. (2011)	Poultry (neck skin)	<i>C. jejuni</i> , <i>C. coli</i>	<i>C. jejuni</i> (CIP, 20.3%; ERY, 2.9%; GEN, 0%; NAL, 69.5%), <i>C. coli</i> (CIP, 7.5%; ERY, 0%; GEN, 2.5%; NAL, 15%).	High antibiotic resistance rate among <i>Campylobacter</i> spp. isolates from retail poultry in Cambodia.
Malaysia	2012	Adzitey et al. (2012)	Duck (carcasses)	<i>C. jejuni</i>	AMP, 81%; CIP, 76%; GEN, 5%; ERY, 1%; NAL, 84%; TET, 96%.	<i>C. jejuni</i> from ducks were resistant to most of the antibiotics tested.
Malaysia	2017	Premarathne et al. (2017)	Cattle (beef)	<i>Campylobacter</i> spp.	AMP, 69%; CIP, 15%; ERY, 31%; NAL, 54%; TET, 77%.	A high percentage of <i>Campylobacter</i> spp. was resistant to TET and AMP.
Philippines	2014	Sison et al. (2014)	Chicken (meat)	<i>Campylobacter</i> spp.	AMP, 77.3%; CIP, 70.4%; ERY, 20.2%; GEN, 11.4%; TET, 54.6%.	The most common combination of MDR (34%) was to AMP, CIP, and TET.
Philippines	2016	Lim et al. (2016)	Chicken (meat)	<i>Campylobacter</i> spp.	ERY, 98.6%; GEN, 65.2%; NAL, 98.1%; TET, 94.2%.	The high rate of resistance of <i>Campylobacter</i> to ERY, NAL, and TET in Manila.

Thailand	2006	Padungtod et al. (2006)	chicken, pigs, dairy cows	<i>Campylobacter</i> spp.	Chicken (AMP, 0%; CIP, 54%; ERY, 6%; GEN, 0%, NAL, 60%, TET, 53%), Pig (AMP, 0%; CIP, 78%; ERY, 83%; GEN, 12%, 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 <i>Campylobacter</i> to FQ, ERY and TET as compared to chicken and dairy cow isolates.
Thailand	2008	Noppon et al. (2008)	Chicken (meat)	<i>C.jejuni</i>	CHL, 13%; DOX, 37%; ERY, 29%; OFX, 91%;	High resistant rate to OFX. More cautious use of OFX and DOX.
Thailand	2009	Noppon et al. (2009)	Chicken (faeces)	<i>Campylobacter</i> spp.	AZM, 6.40%; CIP, 30.37%; CAZ, 0%; CHL, 0%, DOX, 12.65%.	Resistance to antimicrobials would increase with the increasing age of birds.
Thailand	2013	Chokboonm ongkol et al. (2013)	Broiler (caeca and skin)	<i>Campylobacter</i> spp.	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.
Thailand	2015	Charununta korn et al. (2015)	Broiler (cloacal swab)	<i>C.jejuni</i>	AMP, 34.78%; CIP, 95.65%; ERY, 0.69%; GEN, 0%; TET, 84.06%.	Routine monitoring of antimicrobial resistance of <i>Campylobacter</i> in contracted broiler farms.
Thailand	2015	Saengthong pinit et al. (2015)	Duck (cloacal swab)	<i>Campylobacter</i> spp.	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 <i>Campylobacter</i> .
Thailand	2017	Thomrongsu wannakij et al. (2017)	Chicken (cloacal swabs)	<i>C.jejuni</i> , <i>C. coli</i>	<i>C. jejuni</i> (SXT, 81.9%, TET, 97.9%); <i>C. coli</i> (SXT, 36%, TET, 55%)	High level of MDR and high resistance rates to antimicrobials.
Vietnam	2010	Schwan (2010)	Chicken	<i>Campylobacter</i> spp.	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.
Vietnam	2016	Nguyen et al. (2016)	Chicken meat and pork	<i>C.jejuni</i>	CIP, 66.7%; ERY, 25%; GEN, 0%; NAL, 87%; TET, 75%.	Low resistance rate to ERY and GEN.

¹*C. jejuni* (*Campylobacter jejuni*), *C. coli* (*Campylobacter coli*).

²Resistance rate to AZM (azithromycin), ceftazidime (CAZ), CIP (ciprofloxacin), CHL, chloramphenicol, ERY (erythromycin), FQ (fluoroquinolone), GEN (gentamicin), NAL (nalidixic acid), NOR (norfloxacin), STR (streptomycin), SXT (Trimethoprim/sulfamethoxazole), TET (tetracycline).

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