



Review Article

Human campylobacteriosis: A public health concern of global importance

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ABSTRACT

Campylobacter species are among the leading cause of bacterial foodborne and waterborne infections. In addition, *Campylobacter* is one of the major causative agent of bacterial gastrointestinal infections and the rise in the incidence of *Campylobacter* infections have been reported worldwide. Also, the emergence of some *Campylobacter* species as one of the main causative agent of diarrhea and the propensity of these bacteria species to resist the actions of antimicrobial agents; position them as a serious threat to the public health. This paper reviews *Campylobacter* pathogenicity, infections, isolation and diagnosis, their reservoirs, transmission pathways, epidemiology of *Campylobacter* outbreaks, prevention and treatment option, antibiotics resistance and control of antibiotics use.

1. Introduction

Campylobacter belong to a distinct group of specialized bacteria designated rRNA superfamily VI of Class Proteobacteria (Allos, 2011). *Campylobacter* species are slender Gram-negative rod-shaped, spiral-shaped with single or pair of flagella. Some *Campylobacter* species have multiple flagella such as *C. showae* while some species are non-motile like *C. gracilis* (Acke, 2018). *Campylobacter* species are indole negative, oxidase positive, hippurate positive, catalase positive, nitrate positive and glucose utilization negative (Pal, 2017). *Campylobacter* species are closely related group of bacteria that principally colonise the gastrointestinal tracts of different animals (El-Gendy et al., 2013). *Campylobacter* species are enormous significance due to the increase in number of species implicated in animals and human's infections (Jamshidi et al., 2008; Kaakoush et al., 2015). Since its first identification, the number of pathogenic *Campylobacter* species that causes animal and human infections are largely classified through phylogenetic means with few as 500–800 bacteria ingestion dose resulting to human disease (Frirdich et al., 2017; Kaakoush et al., 2009). Nonetheless, report has shown that *Campylobacter* doses of 100 cells or less have been linked with human infections (Tribble et al., 2010). The major infection caused by *Campylobacter* is mainly acute diarrhea (Allos et al., 2013; Blaser, 2008) and since 1977, *Campylobacter* species have been known as the major causative agent of acute diarrhea (Skirrow, 1977). *Campylobacter* species have also been reported to be implicated in various human systemic

infections including septic thrombophlebitis, endocarditis, neonatal sepsis, pneumonia (Alnimr, 2014), bloodstream infections (BSIs) (Morishita et al., 2013), acute colitis of inflammatory bowel disease and acute appendicitis (Lagler et al., 2016). Other major post-infections that significantly add to *Campylobacter* disease burden include severe demyelinating neuropathy, Guillain-Barré syndrome (GBS) (Scallan et al., 2015), sequelae and Miller-Fisher syndrome (MFS) (Skarp et al., 2016). *Campylobacter* species are also associated with series of gastrointestinal infections like colorectal cancer and Barrett's esophagus (Man, 2011). In small group of patients, *Campylobacter* species have also been reported to be associated with extragastrointestinal infections such as brain abscesses, meningitis, lung infections, bacteremia and reactive arthritis (Man, 2011).

Campylobacter is a significant zoonotic causes of bacterial food-borne infection (Hsieh and Sulaiman, 2018) and farm animals are the major reservoir of *Campylobacter* species and the major cause of campylobacteriosis (Grant et al., 2018). Worldwide, farm animals are also the major cause of both bacteria food poisoning (Del Collo et al., 2017) and *Campylobacter* foodborne gastrointestinal infections (Seguino et al., 2018). *Campylobacter* foodborne infection is a problem and an economic burden to human population which caused about 8.4% of the global diarrhea cases (Connerton and Connerton, 2017). *Campylobacter* food-borne infection is a global concern because of the emerging *Campylobacter* species involved in both human infections and *Campylobacter* foodborne outbreaks (CDC, 2014). *Campylobacter* foodborne outbreak is

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defined as *Campylobacter* infection that involve more than two or more persons as a result of consumption of *Campylobacter* contaminated foods (Mungai et al., 2015). Majority of campylobacteriosis cases are not recognized as outbreaks rather as sporadic episode involving a single family group (Del Collo et al., 2017). Campylobacteriosis is a collective name of infections caused by pathogenic *Campylobacter* species and is characterized by fever, vomiting, watery or bloody diarrhea (Scallan et al., 2015). In general, *Campylobacter* infections are predominantly common in certain age group such as children (below 4) and the aged (above 75) (Lévesque et al., 2013). Other group of people at high risk of *Campylobacter* infections are immunocompromised individuals, hemoglobinopathies patients and those suffering from inflammatory bowel disease (Kennedy et al., 2004). In addition, the risks of *Campylobacter* infections are higher in high income nations than in low income nations (Platts-Mills and Kosek, 2014). In low income nations, a number of environmental sources pose a high risks of human *Campylobacter* infections (Lee et al., 2013); and most outbreaks are caused by consumption of poultry meats and poultry products (Taylor et al., 2013). Poultry meats include meats from laying hens, turkeys, ostriches, ducks and broilers (Epps et al., 2013), and poultry meats and its product cause about 60–80% of the global campylobacteriosis cases (EFSA, 2015).

2. Main text

2.1. *Campylobacter* species

Campylobacter species are divided into Lior serotypes and penner serotypes and over 100 Lior serotypes and 600 penner serotypes have been reported. Among these Lior serotypes and penner serotypes, only the thermotolerant *Campylobacter* species have been reported to have clinical significance (Garcia and Heredia, 2013).

2.1.1. Pathogenic *Campylobacter* species

Worldwide, pathogenic *Campylobacter* species are responsible for the cause of over 400–500 million infections cases each year. Pathogenic *Campylobacter* species known to be implicated in human infections includes *C. jejuni*, *C. concisus*, *C. rectus*, *C. hyointestinalis*, *C. insulaenigrae*, *C. sputorum*, *C. helveticus*, *C. lari*, *C. fetus*, *C. mucosalis*, *C. coli*, *C. upsaliensis* and *C. ureolyticus* (Heredia and García, 2018). These pathogenic *Campylobacter* species are grouped into major human enteric pathogens (*C. jejuni*, *C. jejuni* subsp. *jejuni* (Cjj), *C. jejuni* subsp. *doyley* (Cjd), *C. coli* and *C. fetus*); minor pathogens (*C. concisus*, *C. upsaliensis*, *C. lari* and *C. hyointestinalis*) and major veterinary pathogens (*C. fetus* subsp. *venerealis* (Cfv) and *C. fetus* subsp. *fetus* (Cff)) (Rollins and Joseph, 2000).

2.1.2. *C. jejuni*

C. jejuni is a motile, microaerophilic, zoonotic, thermophilic bacterial considered as the leading cause of worldwide foodborne bacterial gastroenteritis (Taheri et al., 2019). It's a member of the genus *Campylobacter* with polar flagella and helical morphology that is used for movement through viscous solutions including the mucus layer of the gastrointestinal tract (Lertsethtakarn et al., 2011). *C. jejuni* is the major enteric pathogen that displays significant strain-to-strain dissimilarities in their pathogenicity patterns (Hofreuter et al., 2006). *C. jejuni* is the major species that caused infections than other pathogenic *Campylobacter* species (Liu et al., 2017) and also the major *Campylobacter* species that regularly cause diarrhea in human (Epps et al., 2013). Infections caused by *C. jejuni* can develop into diverse severities such as mild and self-limiting diarrhea to hemorrhagic colitis and sometimes to meningitis and bacteremia (Burnham and Hendrixson, 2018; Dasti et al., 2010). *C. jejuni* infections are also associated with many secondary complications such as autoimmune neuropathy (Liu et al., 2018), and inflammatory bowel disease (IBD) (Drenthen et al., 2011; Loshaj-Shala et al., 2015). *C. jejuni* is the major *Campylobacter* species that cause disease in young people (Haddock et al., 2010). *C. jejuni* infections can occur via various routes such as through direct contact with companion and farm

animals or through waterborne or foodborne transmission (Domingues et al., 2012). *C. jejuni* is a commensal bacterial of chickens which inhabit the chicken intestines at a level >106–108 CFU/g of chicken faeces (Oh et al., 2018) and chickens are the main vector for human campylobacteriosis (Hartley-Tassell et al., 2018). *C. jejuni* consist of two subspecies; *C. jejuni* subsp. *jejuni* (Cjj) and *C. jejuni* subsp. *doyley* (Cjd) (Man, 2011). The main phenotypic feature generally used to differentiate Cjj from Cjd strain is the inability of *C. jejuni* subsp. *doyley* to reduce nitrate and also, Cjd is also associated with high susceptibility to cephalothin. Clinically, Cjd strain causes both enteritis and gastritis (Parker et al., 2007). *C. jejuni* subsp. *jejuni* (Cjj) is the main bacterial cause of enteroinvasive diarrhea (Pacanowski et al., 2008) and the major symptoms of *C. jejuni* infections include severe enteritis, severe abdominal cramps, fever and bloody diarrhea with mucus (Biswas et al., 2011). In addition, *C. jejuni* has also been reported to be associated with immunoreactive complications like Miller-Fisher syndromes (Dingle et al., 2001).

2.1.3. *C. coli*

Campylobacter coli is an S-shaped curved cell measuring about 0.2–0.5 micrometers long with a single flagellum. It's very similar to *C. jejuni*; and both bacteria cause inflammation of the intestine and diarrhea in humans (Prescott et al., 2005). *C. coli* is the second most regularly reported *Campylobacter* species that causes human infections (Crim et al., 2015). *C. coli* is grouped into 3 clades (clade 1, 2 and 3). *C. coli* clade 1 includes most *C. coli* isolated from humans and farm animals. *C. coli* clade 1 causes most of human infections whereas infections cause by *C. coli* clade 2 and 3 are rare (Johansson et al., 2018). In high income countries, report has shown that *C. coli* is the second most regular cause of campylobacteriosis (Beier et al., 2018). Also in high income countries, *C. coli* infections are usually sporadic and it show seasonal drifts with majority of the infections occurring in early fall or late summer (Allos and Blaser, 2009). The clinical manifestations of *C. coli* infections include watery diarrhea, abdominal pain, vomiting, fever, inflammatory enterocolitis, malaise and nausea (Fitzgerald and Nachamkin, 2007).

2.1.4. *C. fetus*

C. fetus is a curved cell, fastidious motile bacterial that majorly cause septic abortion in farm animals. *C. fetus* can cause infection in human and its infection can be acquired through direct contact with animals, through consumption of undercooked contaminated meat or through ingesting food or water contaminated by animal faeces (Koneman et al., 1997). *C. fetus* is grouped into 3 subsp. which includes: *C. fetus* subsp. *venerealis* (Cfv), *C. fetus* subsp. *testudinum* (Cft) and *C. fetus* subsp. *fetus* (Cff) (Iraola et al., 2017). Cfv and Cff are associated with farm animal infections (Wagenaar et al., 2014); while Cft has also been reported to be associated with human infection such as bacteremia (Fitzgerald et al., 2014). Cff and Cfv are categorized on the basis of their clinical manifestations and mechanisms of transmission (Iraola et al., 2016). Cff caused abortion in infected sheep and cattle (On, 2013) and it's an opportunistic human pathogen that largely infects immunocompromised patients (Wagenaar et al., 2014). Cfv is reported to be cattle-restricted pathogen (Mshelia et al., 2010), but this species has been isolated from humans and most human infection caused by *C. fetus* strain is majorly caused by Cff (Patrick et al., 2013). Some of the major reported symptoms of *C. fetus* infections include endocarditis, meningitis, septicemia, septic arthritis, peritonitis and cellulitis (Hur et al., 2018). *C. fetus* is sometimes responsible for human systemic infections like bloodstream infection in immunosuppressed and immunocompromised individuals (Morishita et al., 2013), but infections are rare (Kienesberger et al., 2014).

2.1.5. *C. lari*

Campylobacter lari was previously called *Campylobacter laridis* and is part of the thermotolerant *Campylobacter* species. *C. lari* is grouped into a genotypically and phenotypically diverse *Campylobacter* group that encompasses of the nalidixic-acid susceptible (NASC) group, nalidixic acid-

resistant thermophilic *Campylobacter*, the urease-positive thermophilic *Campylobacter* and the urease-producing NASC. These aforementioned groups are all identified as variants of *C. lari* group (Duim et al., 2004). This *C. lari* group is made up of five *Campylobacter* species (*C. subantarcticus*, *C. insulaenigrae*, *C. volucris*, *C. lari* and *C. peloridis*) with other group of strains called UPTC and *C. lari*-like strains (Miller et al., 2014). Though, some of these strains formally identified as *C. lari* group were later classified as novel taxa such as *C. volucris* (Debruyne et al., 2010) and *C. peloridis* (Debruyne et al., 2009). *C. lari* is a species within the genus *Campylobacter* and is grouped into two novel subsp. namely; *C. lari* subsp. *concheus* (Clc) and *C. lari* subsp. *lari* (Cll) (Miller et al., 2014). In 1984, *C. lari* was first reported in immunocompromised patient and since then sporadic cases including water-borne *C. lari* outbreaks have been reported (Martinot et al., 2001). *C. lari* has also been reported to be associated with enteritis, purulent pleurisy, bacteremia, urinary tract infection (Werno et al., 2002), reactive arthritis and prosthetic joint infection (Duim et al., 2004).

2.1.6. *C. upsaliensis*

Campylobacter upsaliensis is among the thermotolerant *Campylobacter* species and is mostly found in dogs and cats, regardless of whether the animal is sick or healthy (Jaime et al., 2002). *C. upsaliensis* is the third most *Campylobacter* species after *C. jejuni* and *C. coli*. *C. upsaliensis* was named after the city it was first described and thereafter, reports have emerged globally associating this species as a human bacterial enteropathogen (Bourke et al., 1998). *C. upsaliensis* is a well-known *Campylobacter* species that cause diarrhea in felines and canines (Steinhauserova et al., 2000). *C. upsaliensis* is well recognized as a clinically important emerging diarrhea pathogen in both pediatric and immunocompromised persons (Couturier et al., 2012). It is one of the emerging *Campylobacter* species that is associated with human infections including Crohn's disease, neonatal infection, bacteremia, abscesses, meningitis and abortion (Wilkinson et al., 2018). *C. upsaliensis* has also been reported to cause acute or chronic diarrhea in human and diarrhea in dogs (Cecil et al., 2012) though genetic studies have shown that *Campylobacter* strains isolated from dogs and human strains are different (Damborg et al., 2008). In many nations, *C. upsaliensis* is the second reported *Campylobacter* species that cause infections in human after *C. jejuni* (Premarathne et al., 2017).

2.1.7. Other pathogenic *Campylobacter* species

Other pathogenic *Campylobacter* species implicated in human infections includes *C. mucosalis*, *C. curvus*, *C. insulaenigrae*, *C. doylei*, *C. concisus*, *C. helveticus* and *C. rectus* (Cecil et al., 2012). Beside the well-known pathogenic species, other emerging species such as *C. sputorum* biovar *sputorum*, *C. gracilis*, *C. ureolyticus*, *C. peloridis* and *C. showae*, have also been reported to be implicated in causing human infections with some life-threatening complications in hospitalized patients (Nishiguchi et al., 2017). Some of these emerging *Campylobacter* species have also been isolated and detected in samples from the axillary nerve, soft tissue lesions, hepatic, lung, bone infections, the cerebrospinal, peritoneal fluid, genitalia, brain abscesses and thoracic empyema of hospitalized patients (Magana et al., 2017). In addition to these life-threatening complications caused by these emerging pathogens, there is a huge gap in tracing the connection between infection and source of human infection (Man, 2011). Furthermore, even with the global incidence of *Campylobacter* species in causing infections, the knowledge of the epidemiology and pathogenesis are still incomplete (Nielsen et al., 2006).

3. Pathogenicity of *Campylobacter* species

Campylobacter species are of economic importance as they constantly cause foodborne infections due to diverse genes involved in its pathogenicity (Bolton, 2015). *Campylobacter* pathogenicity is based on the virulence factors (Larson et al., 2008) and these virulence factors are multi-factorial in nature and the ability of these bacteria to survival and

resist physiological stress also contributes to its pathogenicity (Casa-bonne et al., 2016; Ketley, 1995). The various virulence related mechanisms displayed by *Campylobacter* species includes invasive properties, oxidative stress defence, toxin production, iron acquisition and its ability to remain viable but non-culturable state (Bhavsar and Kapadnis, 2006). *Campylobacter* invasion, adherence and colonization also add to the pathogenicity of these groups of bacteria (Backert et al., 2013). Other virulence factors of *Campylobacter* include; secretion of some sets of proteins, translocation capabilities and flagella-mediated motility (Biswas et al., 2011).

3.1. Motility and flagella

Motility is important for *Campylobacter* survival under diverse chemotactic conditions it comes across in the gastrointestinal tract (Jagannathan and Penn, 2005). In some *Campylobacter* species, the motility system with the flagella involves a chemosensory system that steers flagella movement depending on the environmental conditions where these bacteria are found. *Campylobacter* chemotaxis and flagellin are the two important virulence factors that help lead these bacteria to its colonization site and also help in invading the host cell (van Vliet and Ketley, 2001). Some of these *Campylobacter* motility virulence factors and their encoding genes are σ^{54} promoter regulates gene (*flaB*) and σ^{28} promoter regulates gene (*flaA*) (Hendrixson, 2006). The *flaA* gene appears to be significant for invasion, colonization of the host epithelial cells and adherence to the host gastrointestinal tracts (Jain et al., 2008). The flagellum is composed of structural extracellular filamentous components and a hook-basal body. The hook-basal body comprises of the following: (a) the surface localized hook, (b) the periplasmic rod and associated ring structures and (c) a base embedded in the cytoplasm and inner membrane of the cell (Lertsethtakarn et al., 2011). The hook-basal body is a complex component that is made up of a number of diverse proteins such as FliO, FlhA, FliG, FlhB, FlhP, FliF, FliQ, FliR, FliY, FliM and FliN (Carrillo et al., 2004), FlgI, FlgH, FlgE, FliK, FlgE and FliK (Bolton, 2015). The extracellular filament of the flagella is composed of multimers of the protein including flagellin protein (FlaA and FlaB), FlaA (coded by *flaA* gene), and FlaB (coded by *flaB* gene) which is the minor flagellin protein (Lertsethtakarn et al., 2011).

3.2. Chemotaxis

Chemotaxis is a method or system by which motile bacteria sense and move to the direction of more favourable conditions and several pathogenic bacteria uses this practice to invade their hosts (Chang and Miller, 2006). *Campylobacter* chemotaxis virulence factors involve in human infections includes chemotaxis proteins; Che A, B, R, V, W and Z encoded by *cheA*, *cheB*, *cheR*, *cheV*, *cheW* and *cheZ* genes (Hamer et al., 2010), Methyl-accepting chemotaxis proteins encoded by *tlp4*, *tlp* and *tlp1* genes (Marchant et al., 2002), the CheY response regulator that is responsible for controlling flagella rotation encoded by *cheY* gene (Hermans et al., 2011) and *Campylobacter* energy taxis system proteins CetB (Aer2) and CetA (Tlp9) encoded by *cetB* and *cetA* gene (Golden and Acheson, 2002).

3.3. Adhesion

Campylobacter adherence to epithelial cells of the host gastrointestinal tract is a precondition for its colonisation mediated by some adhesins on the bacterial surface (Jin et al., 2001). *Campylobacter* adhesion virulence factors includes outer membrane protein encoded by *cadF* gene, *Campylobacter* adhesion protein A encoded by *capA* gene, phospholipase A encoded by *pldA* gene, lipoprotein encoded by *jlpa* gene, periplasmic binding protein encoded by *peb1A* gene, fibronectin-like protein A encoded by *flpA* and Type IV secretion system encoded by *virB11* gene (Bolton, 2015). *Campylobacter* adhering to fibronectin F is another important *Campylobacter* virulence factor that enables these bacteria to bind to fibronectin which promotes the bacterium-host cell interactions

and colonization (Konkel et al., 2010). Other virulence genes in *Campylobacter* species reported to be linked with human infections responsible for expression of colonization and adherence include *racR*, *dnaJ*, *docA* and *racR* genes (Datta et al., 2003).

3.4. Toxin production

Campylobacter produce different type of cytotoxins and cytolethal distending toxin (CDT) is one of these toxins (Schulze et al., 1998). CDT is a tripartite toxin that is made up of three subunits encoded by the *cdtA*, *cdtB* and *cdtC* genes. Cytolethal distending toxin activity is determined by these three *cdt* cluster genes (Martinez et al., 2006). These three *cdt* cluster genes are all needed for these toxins to be active (Asakura et al., 2008). The *cdtA* and *C* genes are heterodimeric toxin subunits responsible for toxin binding and internalization of the host cell while *cdtB* is the subunit which encodes for the toxic/active components of the toxin (Abuoun et al., 2005). Cytolethal distending toxins induce diarrhea in both humans and animals by intrusive with the division of cells in the intestinal crypts (Carvalho et al., 2013).

3.5. Invasion

Invasion is another virulence mechanism in *Campylobacter* that is carried out by the flagella which also function as an export apparatus in the secretion of non-flagella proteins during host invasion (Poly and Guerry, 2008). There are many virulence genes that are involved in *Campylobacter* invasion mechanism and the products of these genes including flagellin C (*flaC*) and invasion antigens (*cia*) genes. These genes are transported into the host cell's cytoplasm with the aid of flagella secretion system which is vital for invasion and colonisation (Konkel et al., 2004). The secretion of invasion antigens and invasion protein B (*ciaB*) are also important virulence proteins synthesized by *Campylobacter* species which help in the epithelial cells invasion and adhesion of the host gastrointestinal tract (Casabonne et al., 2016). Other important virulence genes and proteins synthesized by *Campylobacter* species including the 73-kDa protein involved in adhesion, the invasion antigen C protein involved in full invasion of INT-407 cells, invasion associated protein gene (*iamA*) implicated in invasion and virulence, the periplasmic protein HtrA responsible for full binding to the epithelial cells, the HtrA chaperone implicated in full folding of out outer membrane protein, the *CiaI* gene implicated in intracellular survival (Bolton, 2015) and *pldA* and *hcp* genes responsible for the expression of invasion (Iglesias-Torrens et al., 2018).

3.6. Other virulence mechanism in *Campylobacter* species

Other virulence mechanism that adds to *Campylobacter* pathogenicity is the ability to obtain the necessary nutrient iron needed for its growth from the host body fluids and tissues (van Vliet and Ketley, 2001). Sialyltransferases (*cstII*) activity also add to *Campylobacter* pathogenicity by providing lipooligosaccharide with a defensive barricade that help facilitates in the disruption of the epithelial cells which mimic the action of human ganglioside inducing diarrhea (Pérez-Boto et al., 2010). The *wlaN* gene is implicated in lipopolysaccharide production (Wieczorek et al., 2018). The *spot* gene is responsible for extreme control (Gaynor et al., 2005), the Kat A (catalase) responsible to convert H₂O₂ to H₂O and O₂ (Bingham-Ramos and Hendrixson, 2008), the *cj0012c* and *cj1371* proteins genes implicated to protect against reactive oxygen species (Garreaux et al., 2008). The Peb4 chaperone is another virulence mechanism in *Campylobacter* that play a significant role in the exporting of proteins to the outer membrane (Kale et al., 2011). Other virulence genes responsible for stress response genes includes the *cosR*, *cj1556*, *spoT*, *ppk1*, *csrA*, *nuoK* and *cprS* and the cell surface modifications genes (*waaF*, *pgp1* and *peb4*) (García-Sánchez et al., 2019). All these aforementioned *Campylobacter* virulence-associated genes have all been reported to be implicated in human infections (Hansson et al., 2018).

4. *Campylobacter* infections

Campylobacter are types of bacteria that majorly cause infections in the gastrointestinal tract. *Campylobacter* infections may be acquired through different means including consumption of unpasteurized milk, non-chlorinated/contaminated surface water and consumption of undercooked poultry or red meat. *Campylobacter* infections can also be acquired through direct contact with infected pets within the family environment (Shane, 2000). The clinical manifestations of *Campylobacter* infections are oftentimes impossible to differentiate from infections caused by *Shigella* and *Salmonella* (Hansson et al., 2018). *Campylobacter* mechanisms of survival and infection is poorly understood but when colonized the ileum, jejunum and colon, it sometimes causes infection with or without symptoms. Fig. 1 is a schematic representation of the transmission cycle involve in *Campylobacter* infection.

4.1. Classification of *Campylobacter* infections

Campylobacter infection is a bacterial infection that commonly causes human gastroenteritis but infection can also occur outside the intestines. *Campylobacter* infections are classified into two categories namely; (i): Gastrointestinal infection (GI) and (ii): Extragastrointestinal infection.

4.1.1. Gastrointestinal infections

Gastrointestinal infection (GI) is the inflammation of the gastrointestinal tract involving both the small intestine and stomach (Walsh et al., 2011). GI is generally characterized by diarrhea (Kaakoush et al., 2015). *Campylobacter* is 1 of the 4 key global bacterial cause of gastrointestinal infections (WHO, 2018). It's also the major and regular cause of traveler's diarrhea (Bullman et al., 2011) and children diarrhea (Liu et al., 2016). Besides diarrhea, other gastrointestinal infections associated with different *Campylobacter* species are shown in Table 1.

4.1.2. Extragastrointestinal infections

Extragastrointestinal infections (EI) are infections outside the intestines but symptoms are associated with a problem within the intestine (Hernandez and Green, 2006). Extragastrointestinal infections reported to be associated with *Campylobacter* infections includes reactive arthritis, GBS (Kuwabara and Yuki, 2013), bacteremia, septicaemia (Man, 2011), septic arthritis, endocarditis, neonatal sepsis, osteomyelitis, and meningitis (Allos, 2001). In small number of cases, other extragastrointestinal post-infections associated with *Campylobacter* infections include severe neurological dysfunction, neurological disorders and a polio-like form of paralysis (WHO, 2018). Some *Campylobacter* species associated with extragastrointestinal infections are listed in Table 2.

4.2. Isolation and diagnosis of *Campylobacter* infection

Isolation of *Campylobacter* species relied on culture-based methods which have helped to strongly ascertain its part in human infections (Moore et al., 2005). *Campylobacter* isolation involves a medium that uses antibiotics as selective agents. These antibiotics used differs from a single antibiotic including cefoperazone or cefazolin in modified CDA medium to a "cocktail" of polymyxin B, trimethoprim and vancomycin found in Skirrow's medium (Thomas, 2005). *Campylobacter* sensitivity to oxidizing radicals and O₂ has led to the development of a number of selective media and selective agents for its isolation (Silva et al., 2011). Before the development of these culture media for *Campylobacter* isolation and detection, non-selective medium was previously used but the medium was less proper for isolation of campylobacters from environmental and animal samples. Owing to this problem, Bolton and Robertson in 1977 developed a selective Preston medium suitable for *Campylobacter* isolation from environmental and food samples (Bolton and Robertson, 1982). Several other selective broths and media latter developed for *Campylobacter* isolation includes Bolton broth, Preston broth and *Campylobacter* enrichment broth (Baylis et al., 2000), modified charcoal cefoperazone

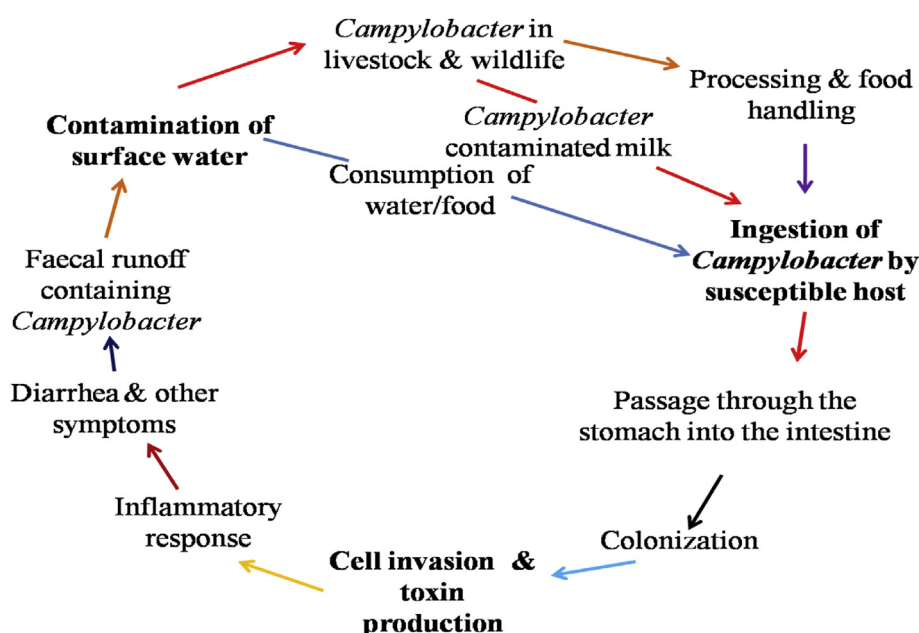


Fig. 1. Overview of the transmission cycle involve in *Campylobacter* infections.

deoxycholate agar (mCCDA) (Wei et al., 2018), CampyFood agar (CFA) and broth, RAPID *Campylobacter* agar (Seliwiorstow et al., 2014), *Campylobacter* agar base (CAB) and *Campylobacter* Cefex agar (Kashap-panavar et al., 2018). *Campylobacter* species are microaerobic, fastidious bacteria capable of growing in a temperature between 37 °C and 42 °C (Davis and DiRita, 2017). Despite *Campylobacter* sensitivity to high temperature and low oxygen concentration, the actual procedures used by clinical laboratories in its isolation from human faecal specimens may vary in different countries (Hurd et al., 2012). However, laboratory diagnosis of campylobacteriosis is usually carried out by culture-base technique or by rapid detection of *Campylobacter* antigen (Enzyme Immunoassay) in stool samples, body tissue or fluids of infected person to identify the genetic materials of this bacterial strain that shows similar symptoms with other bacteria pathogens (Adedayo and Kirkpatrick, 2008; do Nascimento et al., 2016).

Other method use for *Campylobacter* identification includes growth morphology, biochemical tests (Prouzet-Mauléon et al., 2006) and some of these identification methods used are not unreliable (On, 2001). However, other molecular techniques have been designed as alternative and better diagnostic methods for identification (Kuijper et al., 2003). In 1992, application of polymerase chain reaction (PCR) was first used for specific detection of *C. coli* and *C. jejuni* (Oyofo et al., 1992), and PCR is

widely used in the detection and identification of this bacterial to species level (Shawky et al., 2015). In addition to PCR techniques, other molecular methods used for identification or detection of *Campylobacter* species include random amplified polymorphic DNA (da Silva et al., 2016), whole-genome sequencing (Hasman et al., 2014; Schürch et al., 2018), matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) (Patel, 2019; Singhal et al., 2015). Some of the challenges involved in *Campylobacter* isolation and identification includes difficult procedures for isolation and identification (Llarena et al., 2017), sub-optimal storage and loss of isolates during extensive freeze-thaw cycles which has raised concerns to the scientific community (Maziero and de Oliveira, 2010). Likewise, the presence of the “protective guard” in a community of multispecies biofilm could hide a wide range of emerging pathogenic *Campylobacter* species which can successfully “escape” adverse environments and regain its ability to cause infection when found in optimal conditions may lead to wrong results in the diagnosis process (Wood et al., 2013). Another serious challenge for public health concern in campylobacters identification and diagnosis is its ability to remain viable but nonculturable but retain its physiology and virulence ability (Ayrapetyan and Oliver, 2016; Li et al., 2014). Lasstly, the

Table 1

Campylobacter species associated with human gastroenteritis.

<i>Campylobacter</i> species	Gastrointestinal infections
<i>C. coli</i>	Gastroenteritis and acute cholecystitis
<i>C. concisus</i>	Gastroenteritis and Barrett esophagitis
<i>C. curvus</i>	Liver abscess, Barrett esophagitis and gastroenteritis
<i>C. fetus</i>	Gastroenteritis
<i>C. helveticus</i>	Diarrhea
<i>C. hominis</i>	Ulcerative colitis and Crohn's disease
<i>C. hyointestinalis</i>	Diarrhea and gastroenteritis
<i>C. jejuni</i>	Acute cholecystitis and celiac disease
<i>C. insulaenigrae</i>	Abdominal pain, diarrhea and gastroenteritis
<i>C. lari</i>	Gastroenteritis and septicaemia
<i>C. mucosalis</i>	Gastroenteritis
<i>C. rectus</i>	Ulcerative colitis, gastroenteritis and Crohn's disease
<i>C. showae</i>	Ulcerative colitis and Crohn's disease
<i>C. sputorum</i>	Gastroenteritis
<i>C. upsaliensis</i>	Gastroenteritis
<i>C. ureolyticus</i>	Gastroenteritis, Crohn's disease and ulcerative colitis

Table 2

Campylobacter species associated with human extragastrointestinal infections.

<i>Campylobacter</i> species	Extragastrintestinal infections
<i>C. coli</i>	Bacteremia, sepsis, meningitis and spontaneous abortion
<i>C. concisus</i>	Brain abscess, reactive arthritis and rheumatoid arthritis
<i>C. curvus</i>	Bronchial abscess and bacteremia
<i>C. fetus</i>	Meningitis, vertebral osteomyelitis, brain abscess, cellulitis, septic abortion and bacteremia,
<i>C. hominis</i>	Bacteremia
<i>C. hyointestinalis</i>	Fatal septicaemia
<i>C. jejuni</i>	Sequelae such as bacteremia, urinary tract infection, GBS, reactive arthritis, MFS, sepsis, meningitis and hemolytic uremic syndrome
<i>C. insulaenigrae</i>	Septicemia
<i>C. lari</i>	Bacteremia
<i>C. rectus</i>	Necrotizing soft tissue infection and empyema thoracis
<i>C. showae</i>	Intraorbital abscess
<i>C. sputorum</i>	Axillary abscess and bacteremia
<i>C. ureolyticus</i>	Reactive arthritis and rheumatoid arthritis
<i>C. upsaliensis</i>	Breast abscess, bacteremia and spontaneous abortion

laboratory diagnosis of *Campylobacter* infections caused by other pathogenic *Campylobacter* species except *C. coli* and *C. jejuni* is complex due to the challenging growth and identification processes of the several subsets of *Campylobacter* species (Magana et al., 2017).

4.3. Transmission routes of *Campylobacter* infection

Campylobacter species majorly colonized the intestine of poultry, European blackbirds, cattle, sheep, ostriches, cats, dogs and pigs (Dearlove et al., 2016). These bacteria are shed in the faeces of these animals into the environment (Goni et al., 2017). *Campylobacter* can also spread to person by direct contact to animals such as pets (ESR, 2016; Westermarck, 2016), with dog owners at high risk of *Campylobacter* infection (Gras et al., 2013). Beside pets, other domestic animals such as cattle are also regularly colonized by *Campylobacter* species and persons working with these animals are also at high risk of *Campylobacter* infection (Hansson et al., 2018). Other sets of people at high risk of campylobacteriosis include farms and abattoirs workers who sometimes do not practice hand-washing and food safety habits (Aung et al., 2015). However, identification and understanding the transmission routes of *Campylobacter* infections is crucial for its prevention and control (Newell et al., 2017). The common and major route/pathways of campylobacteriosis includes through faecal-oral routes (Rosner et al., 2017), through consumption of contaminated undercooked meats or through consumption of contaminated food/water (Grzybowska-Chlebowczyk et al., 2013). Fig. 2 is a schematic illustration of overview of the transmission routes of *Campylobacter* infection.

4.3.1. Milk as a route of *Campylobacter* transmission

Worldwide, there is a rise in the consumption of unpasteurized milk as a result of its health benefits compared to pasteurized milk (Sugrue et al., 2019). Despite the health benefits in the consumption of unpasteurized milk, there is a great concern to the health risk its pose to human (Baars et al., 2019). Milk is a white liquid and a nutrient-rich food produced in the mammary glands of mammals. It's a source of protein, dietary fats and minerals (calcium and magnesium) for growth particularly

in children (O'Callaghan et al., 2019). Milk is consumed either unpasteurized or pasteurized and mammals that produced milk for human consumption includes sheep, buffalo, goats, cows, yak and camel and the highest proportions of commercially produced milks are from cows (Quigley et al., 2013). Milk is considered germ-free when secreted in the alveoli of the udder (Vacheyrou et al., 2011). Fresh milk drawn from animals naturally possess a short lived antibacterial system that display 'germicidal' or 'bacteriostatic' properties but bacterial growth is inevitable after sometimes except it undergoes heat treatment or freezing (Sarkar, 2016). Milk is a good substrate for bacteria growth (Hudson et al., 2014) and it's reported to be among the major transmission routes for *Campylobacter* to humans (El-Zamkan and Hameed, 2016). Milk is natural foods that has no protection against external contamination and can easily be contaminated when separated from its source (Neeta et al., 2014). Milk contamination generally occurs from environmental sources such as water, grass, milking equipments, feed, air, teat apex, soil and other sources (Coorevits et al., 2008). It's believed that the occurrence of *Campylobacter* species in raw milk samples is from faecal contamination (Oliver et al., 2005). *Campylobacter* species have been detected in cow milk (Del Collo et al., 2017 et al., 2017), and different *Campylobacter* species that have been detected in milk samples from different mammals including *C. Jejuni* detected in buffalo and cow milk (Modi et al., 2015) and *C. coli* identified in cow milk (Rahimi et al., 2013). *Campylobacter* species have also been detected in bulk tank milk where these milks are stored (Bianchini et al., 2014), and *Campylobacter* species reported to have been detected from milk samples from the bulk tank include *C. lari*, *C. jejuni* and *C. coli* (Del Collo et al., 2017). Globally, several cases of illness and deaths have been reported to occur via consumption of contaminated raw milk and its products (Hati et al., 2018), and in many countries, milk-borne pathogens are of public health concern (Amenu et al., 2019).

4.3.2. Meat as a route of *Campylobacter* transmission

Worldwide, consumption of meats is steadily increasing and meats are sometimes contaminated with microorganisms but bacteria contaminations may sometimes occur from animal microbiota, equipment

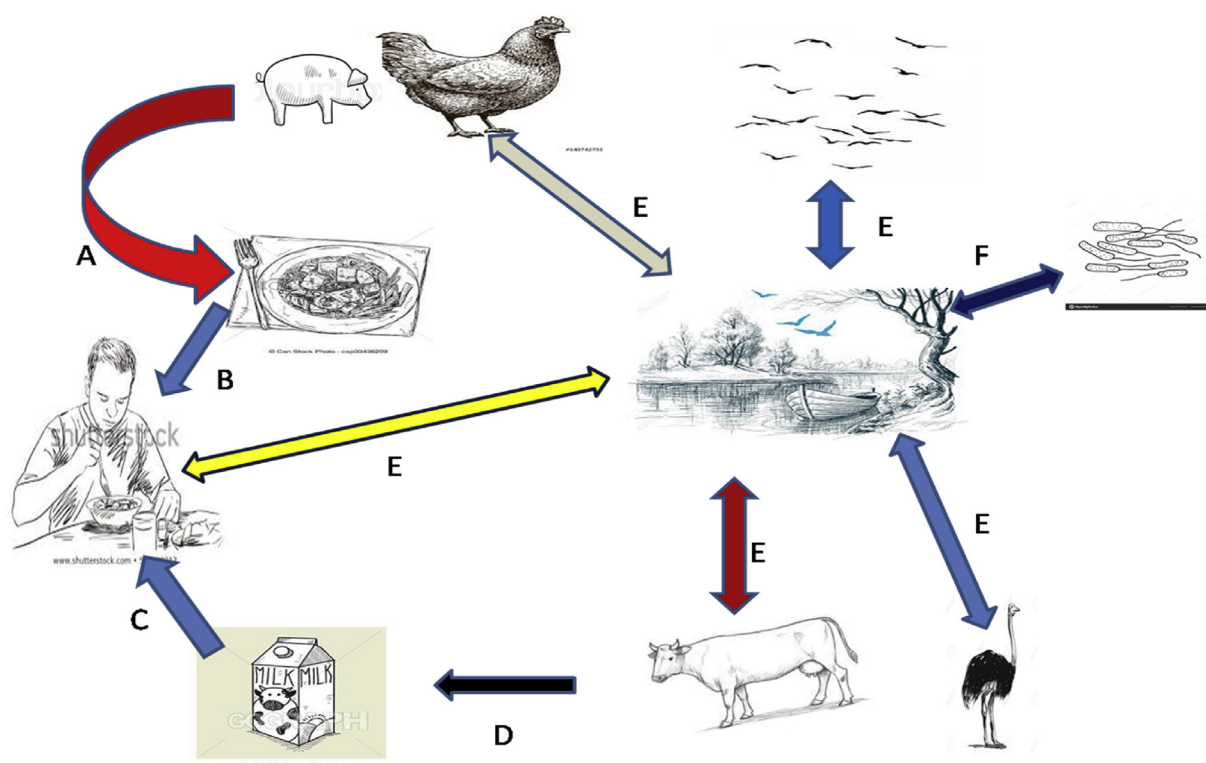


Fig. 2. Overview of the transmission routes of *Campylobacter* infection.

surfaces and water (Vihavainen et al., 2007). The bacteria from animal's microbiota that majorly contaminate meats include pathogenic *Salmonella* and *Campylobacter* species and these two bacteria species are majorly responsible for human gastroenteritis as a result of consumption of contaminated undercooked meat (Rouger et al., 2017). *Campylobacter* contamination remains the major cause of bacterial food-borne infection and the major reservoir of these bacteria species are poultry (Wieczorek et al., 2015). Infections caused by poultry consumption represents about 50–70% of the global *Campylobacter* infections cases (Seliwiorstow et al., 2015), and poultry is define as meats from chicken, turkey, duck and goose (Szosland-Faltyn et al., 2018). Beside poultry, *Campylobacter* species have also been detected in other meat typss such as pork and beef (Hussain et al., 2007; Korsak et al., 2015), mutton (Nisar et al., 2018) and in camel, lamb and chevon (Rahimi et al., 2010). *Campylobacter* species that have been isolated and detected in meat samples include *C. coli* and *C. jejuni* identified in poultry meat (Mezher et al., 2016), *C. coli*, *C. lari*, *C. jejuni* and *C. fetus* detected in mutton samples (Sharma et al., 2016), and *C. jejuni* and *C. coli* detected in pork, beef and lamb (Wong et al., 2007). Isolation and detection of these bacteria species from meats samples position them as one of the major transmission route (Duarte et al., 2014).

4.3.3. Water as a route of *Campylobacter* transmission

Worldwide, access to safe drinking water is one of the targets goals, but report from regular analysis of water samples have showed that unsafe drinking water remain the number eight leading risk factor for human disease (Khan and Bakar, 2019). Studies have also showed that improved water sources including public taps/standpipes, protected dug wells, boreholes and protected springs are not automatically free of faecal contamination (Bain et al., 2014). In high income countries, water is sometimes contaminated through faulty pumps and pipes while in low income countries, majority of the people rely mostly on streams, lakes and other surface water sources for food preparation, washing clothes, drinking and these water are usually contaminated by human and animal faeces exacerbating the possibility of waterborne infections (Thompson and Monis, 2012). Though, some environmental sources used for recreational purposes are often overlooked as a route of disease transmission (Henry et al., 2015). Water is an important route of *Campylobacter* transmission to humans resulting to waterborne infections (Mossong et al., 2016) and waterborne infections can involve several persons (Pitkänen, 2013). Besides, *Campylobacter* infection via consumption of contaminated food/tap water (Irena et al., 2008), other water sources including dug well water have been reported to be implicated in *Campylobacter* outbreaks (Guzman-Herrador et al., 2015). Some of the reported pathogenic *Campylobacter* species detected in water samples from beach and river include *C. coli*, *C. jejuni* and *C. lari* (Khan et al., 2013). Other water sources where these bacteria have also been isolated includes ponds, streams, lakes (Sails et al., 2002), children's paddling pool (Gözl et al., 2018), groundwater and seawater (Kemp et al., 2005).

4.4. Epidemiological information of *Campylobacter* outbreaks

The reports in the incidences of *Campylobacter* outbreaks differs among countries and the true nature of the global occurrence rate is largely unknown (WHO, 2013). The reasons for lack of true incidences rate of *Campylobacter* outbreaks includes underreporting of *Campylobacter* infection cases, differences in the reporting systems, difficulties with diagnosis and differences in surveillance in case of outbreaks (Hansson et al., 2018). *Campylobacter* outbreaks are usually either from waterborne or foodborne infection involving several persons (Frost et al., 2002), and majority of *Campylobacter* outbreaks are usually from animal origin (Wilson et al., 2008). Although, in low income countries, *Campylobacter* outbreaks are majorly from environmental sources such as streams and river where many people depend on these water bodies as their major drinking water source (Clark et al., 2003; Platts-Mills and Kosek, 2014). Beside involvement of water sources in human infection in

low income countries, water sources have also been reported to be implicated in *Campylobacter* outbreaks in high income countries such as Norway (Jakopanec et al., 2008), New Zealand (Bartholomew et al., 2014), Canada (Clark et al., 2003), Finland (Kuusi et al., 2004) and Denmark (Kuhn et al., 2017). *Campylobacter* milk borne infection and outbreaks have also been reported in several high and low income countries (García-Sánchez et al., 2017). Some of the countries with records of campylobacteriosis outbreaks including the Netherlands (Bouwknegt et al., 2013), Israel (Weinberger et al., 2013), China (Chen et al., 2011), Japan (Kubota et al., 2011), India (Mukherjee et al., 2013), Sweden (Lahti et al., 2017), Mexico (Zaidi et al., 2012) and the United States (Geissler et al., 2017; Gilliss et al., 2013). Also, other nations where there have been records of *Campylobacter* outbreaks includes Canada (Keegan et al., 2009; Ravel et al., 2016), British Columbia (Stuart et al., 2010), Australia (Kaakoush et al., 2015; Unicomb et al., 2009), the United Kingdom (Tam et al., 2012), Belgium (Braeye et al., 2015), Denmark (Nielsen et al., 2013), Germany (Hauri et al., 2013), Norway (Steens et al., 2014), Poland (Sadkowska-Todys and Kucharczyk, 2014), New Zealand (Berger, 2012; Sears et al., 2011), Madagascar (Randremanana et al., 2014), Malawi (Mason et al., 2013), Kenya (O'Reilly et al., 2012; Swierczewski et al., 2013), Iceland and Estonia (Sarp et al., 2016), Guatemala (Benoit et al., 2014) and Peru (Lee et al., 2013). Fig. 3 is a map showing records of some reported cases of *Campylobacter* outbreaks in some countries of the world.

4.5. Prevention and treatment of *Campylobacter* infections

Prevention of *Campylobacter* infections can be directly applied to humans by different ways including sewage sanitary conditions, provision of portable water, vaccine usage, public awareness concerning the significance of pasteurization of milk, proper cooking of food from animal origins and the use of therapeutics in case of infections (Hansson et al., 2018). Prevention of *Campylobacter* infections can also be directed on animals by phage treatment (Borie et al., 2014), probiotics, prebiotics, and by improved biosecurity such as the provision of good water quality at farm level and also by monitoring the regular use of antibiotics in animal husbandry. Another vital preventive measure that will help lower the level of these bacteria is the withholding of feed from poultry for about 12 h before slaughter (Hansson et al., 2018). *Campylobacter* infections are sometimes self-limiting but in most cases fluid and electrolyte replacement are major supportive measures for the treatment of this infection (Guarino et al., 2014). Beside fluid and electrolyte replacement, antibiotics are used when symptoms persist and antibiotics treatments are most effective when started within three days after onset of illness. Nonetheless, antibiotics are regularly used in *Campylobacter* infected patients with diarrhea, high fever or patients with other severe illness like weakened immune systems, AIDS, thalassemia, and hypogammaglobulinemia (CDC, 2016). Antibiotics drugs of choice for the treatment of campylobacteriosis includes fluoroquinolones, aminoglycosides, tetracycline, macrolides, betalactams (Bolton, 2015) and erythromycin (Bardon et al., 2009). Other useful alternative antibiotics drugs of choice include ciprofloxacin, vancomycin (Bruzzese et al., 2018) and quinolones (Gilber and Moellering, 2007).

4.6. Antibiotic resistance

Antibiotics use for the treatment of campylobacteriosis is significant for patients with prolonged or severe infections (Reddy and Zishiri, 2017). *Campylobacter* resistance to vital antibiotics used in the treatments of *Campylobacter* infections is an emerging global burden and *Campylobacter* resistance to drugs of choice may limit the treatment options (De Vries et al., 2018). The global spread of antibiotic-resistant *Campylobacter* strains is a continuous process due to the regular use of antibiotics in animal husbandary and this is a problem of public health concern (Silva et al., 2011). Other problems that add to the spread of *Campylobacter* resistance includes inability to completely remove these

antibiotic-resistant bacteria during wastewater treatment process, improper dumping of humans and animals waste into waterbodies and inappropriate preparation of food from animal origin (Founou et al., 2016). Antibiotic resistant bacteria is a global problem associated with increased healthcare cost, prolonged infections with a greater risk of hospitalization and high mortality risk and rate (Founou et al., 2017). Molecular detection of antibiotic resistance genes in *Campylobacter* species have helped in determining the resistance genes in *Campylobacter* species from animals and environmental origin (Moyane et al., 2013). Molecular detection of antimicrobial resistance genes in *Campylobacter* originating from foods and water samples is a major public health concern of global importance (Elhadidy et al., 2018). Some of the resistance genes detected in *Campylobacter* species includes quinolone resistance-genes (*gyrA*, *gyrB* and *parC*) (Piddock et al., 2003), FQ-resistant (*parE*) (Luangtongkum et al., 2009), β -lactamase (*bla_{OXA-61}* and *bla_{OXA-184}*), tetracycline resistance genes (*tetA*, *tetB*, *tetM*, *tetO* and *tetS*) (Reddy and Zishiri, 2017), aminoglycoside resistance genes (*aphA* and *aadE*) (García-Sánchez et al., 2019) and erythromycin resistance gene (*ermB*) (Wang et al., 2014). Antibiotics resistance genes in *Campylobacter* are either acquired by spontaneous mutations or through horizontal gene transfer via transduction, conjugation and transformation (Kumar et al., 2016). Other resistance mechanisms developed by *Campylobacter* against antimicrobials include genetic mutation (Reddy and Zishiri, 2017), point mutation (Luangtongkum et al., 2009), decreased in membrane permeability due to MOMP (García-Sánchez et al., 2019) and rRNA methylases (Wang et al., 2014). Resistance-nodulation-cell division efflux system, modification of ribosomal target sites and weakening of the interaction of the macrocyclic ring and the tunnel wall of the ribosome are also essential resistance mechanism developed in *Campylobacter* (Wei, and Kang, 2018). Fig. 4 is a schematic illustration of the patterns implicated in the spread of antibiotic resistance genes.

4.7. Control of antibiotic use

The emergence of antibiotic-resistant *Campylobacter* strains has rise markedly in both developing and developed countries suggesting the use of antibiotics in animal husbandry as the source of the accelerating trend (Wieczorek and Osek, 2013). Several countries have policy in the control of antibiotics use in animal production (Maron et al., 2013). However, multiples countries do not have policy in the control of antibiotics use for animal production. In addition, grain-based feeds and water are mostly supplemented with antibiotics and other drugs for animal production (Sapkota et al., 2007). In some countries that practise indiscriminate use of antimicrobial in animal production, new regulatory policy should be place on the use of antibiotic in animal husbandry for non-therapeutic reasons such as promoting weight gains of birds or improving feed efficiency (Rahman et al., 2018). Owing to the increase in antibiotic-resistant *Campylobacter* strains, vaccine development is important and vaccination of birds against *Campylobacter* could help eradicate *Campylobacter* from birds and reduce the rate of incidence of human infections (Avci, 2016). Vaccine would also help to reduce high cost of post-harvest treatments (Johnson et al., 2017). Nevertheless, the cost of *Campylobacter* infections treatment to public health systems is high thus the main motivation towards developing a *Campylobacter* vaccine would be to reduce the high costs of treatment associated with campylobacteriosis, enhance food safety and reduce potential human health risks (Lund and Jensen, 2016). Presently, there are no vaccines approved by any global governing authority to prevent *Campylobacter* infections (Riddle and Guerry, 2016). Vaccine approaches against *Campylobacter* infections are restricted by lacking in comprehension of its association with post-infectious syndromes, antigenic diversity, protective epitopes and its pathogenesis (Riddle and Guerry, 2016).

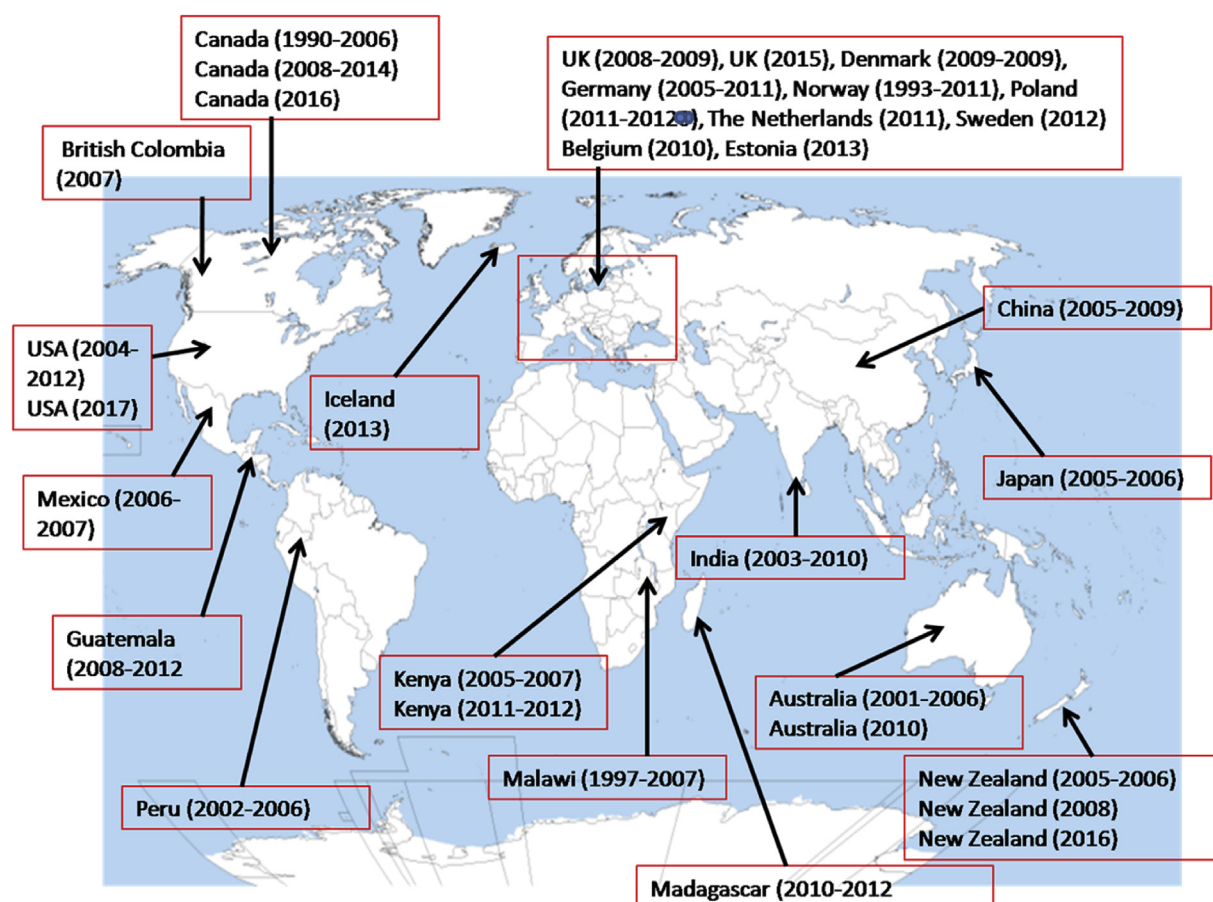


Fig. 3. List of some countries with records of campylobacteriosis outbreaks.

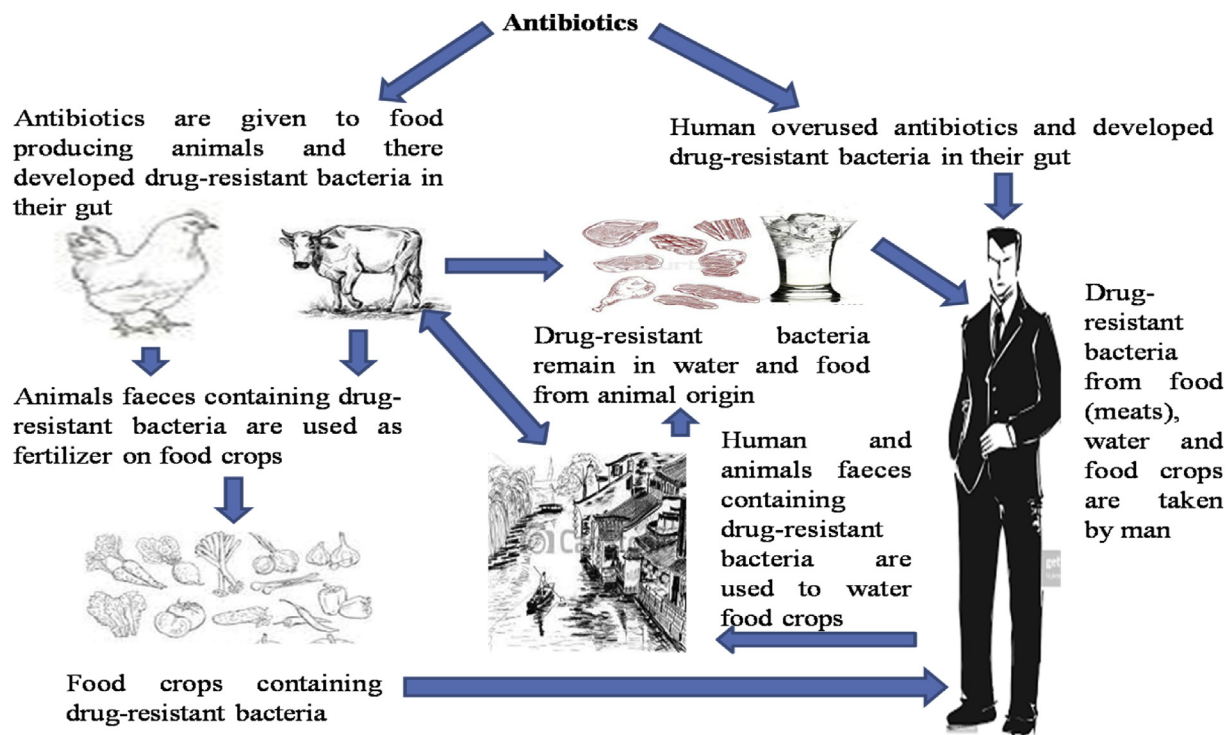


Fig. 4. A schematic process involved in the spread of antibiotic resistance bacteria.

5. Conclusions

Worldwide, outbreaks of campylobacteriosis have been increasing and the major routes of transmission of these bacteria to human is generally believed to be through consumption of contaminated foods. The development of rapid Kits for *Campylobacter* detection and quantification in foods from animal origin will be essential for the prevention of *Campylobacter* infections. *Campylobacter* infections are majorly treated with antibiotics and the actions of these antibiotics have been compromised and this call for the development of new vaccines that will help to control the regular use of antibiotics in animal husbandry. In addition, regular domestic hygiene will also help to prevent *Campylobacter* infections. The production of new and effective antibiotic for better treatment of campylobacteriosis will as well help in the reduction of antibiotic-resistant *Campylobacter* strain and the spread of antibiotics resistant genes.

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