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Clostridium difficile Infection (CDI) in Human-Animal Interface: A One Health Perspective

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Received: Oct 20, 2022 Accepted: Dec 25, 2022

INTRODUCTION

A complex flux of microbes colonizes our gastrointestinal tract (GIT) from the day we are born. The balance of the symbiotic relationship between the intestinal epithelium and the bacterial, fungal, and parasitic microflora is pivotal for good health at any point in the life. Oral contamination of food particles, aided by broncho mucociliary transportation, is digested and sterilized in the stomach's acidic environment. Incursion, beyond this stage is dependent on stomach pH and microbes' capability to transit as resilient spores or stay concealed in mucus membranes. Passage through the small intestine causes a lumen multiplication of around 10^6 bacteria per milliliter reaching the colon, where aqueous resorption raises the concentration to 10^{12} bacteria per gram of fecal matter. Because of the luminal gap between the mucosal oxygenic vessels, the microenvironment favors a thousand to ten thousand fold for most of the anaerobes (Novogrudsky and Plaut 2003).

Clostridium and Bacteroides-Prevotella account for roughly 99 % of all anaerobic bacteria found in the colon (Mai and Morris 2004). Throughout all ages, gut homeostasis relies upon non-motile and enterocytic bacterial interactions, involving cellular adhesion and immunological regulation. The term "colonization resistance" is often used to describe this defensive condition of the natural intestinal ecology (Britton and Young 2014; Murray et al. 2020). Pathogens such as *Clostridium (C.) botulinum*, *C. perfringens* and *C. tetani* produce potent toxins that cause devastating human diseases, including food poisoning, gas gangrene, and tetanus (Khan et al., 2021). *C. difficile* is a prominent enteric pathogen that causes colitis and toxin-mediated diarrhoea, known as *C. difficile*-associated diarrhoea (CDAD) or *C. difficile* infection (CDI). CDI has traditionally been regarded as a hospital-associated disease (Feuerstadt et al. 2023). Even though the earliest outbreaks of *C. difficile*-associated diarrhoea were linked to clindamycin usage, it wasn't until the advent and extensive utilization of broad-spectrum 3rd generation cephalosporins, a class of antibiotic to which *C. difficile* is innately resistant (Slimings and Riley 2014). Pulsed-field gel electrophoresis type NAP1/ restriction endonuclease analysis group BI/PCR ribotype (RT) 027, a "hypervirulent" fluoroquinolone-resistant strain of *C. difficile*, was identified as being North American in origin based on the typing method (He et al. 2013), causing a sharp 4-fold rise in CDI prevalence in Canada and a tripling of fatality rates. The global prevalence of CDI keeps rising in several high income per capita nations (Slimings et al. 2014; Lessa et al. 2015).

Furthermore, a 'novel' characteristic of CDI has emerged. Formerly infrequent community-associated CDI (CA-CDI), described as symptoms beginning in the public and no prior hospitalization in the preceding twelve weeks or symptom onset within 48 hours of hospitalization, has surfaced as a significant percentage of all CDI infections. In the United States, CA-CDI accounts for 41% of all CDI incidence, a 4-fold rise over the last two decades (Khanna et al. 2012). For instance, in 2011, CA accounted for one-third of all the CDI cases in Australia (Slimings et al. 2014), with a rising number of instances over time, from approximately 12% in 2010 to 27% in 2014 (Worth et al. 2016). Interestingly, CA-CDI cases often lack the usual CDI risk factors. They are predominantly young, female, and healthy, with no prior interactions with healthcare facilities or hospitalized individuals and frequently with no record of antibiotic usage (Kuntz et al. 2011). *C. difficile* prefers to thrive in the GIT of mammals (including humans and animals). The bacteria most likely colonize the GIT of all neonate animals, multiply, and are excreted to begin the cycle again by infecting another newborn. As the young One grows older and begins to take a grownup diet, multiple microbes colonized the GIT and the predominance of *C. difficile* declines as other species outdo it (Moono et al. 2016). The use of antibiotics, particularly those that have an action against commensal gut flora, develops an environment that imitates the GIT of infants, which favors *C. difficile* proliferation. Since the 1960s, antibiotics have been administered and used in meat-

Citation: Zafar S, Khan MUZ, Mahmood MS, Abbas RZ, Akram MN, Anwar MN, Arshad MI, Aslam R, Chouhdary M, Fatima N and Ali S, 2023. *Clostridium difficile* Infection (CDI) in Human-Animal Interface: A One Health Perspective. In: Abbas RZ, Saeed NM, Younus M, Aguilar-Marcelino L and Khan A (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 2, pp: 201-208. https://doi.org/10.47278/book.oht/2023.61

producing animals as growth promoters (AGPs) and as a dubious disease prevention tool. (Ronquillo and Hernandez 2017) and consequently, food animals become a significant reservoir and a host for amplification for *C. difficile* (Diaz et al. 2018; Knight and Riley 2019). After 2010, a sharp increase in *C. difficile* contaminates food and the environment (Diaz et al. 2018; Knight and Riley 2019). Recent developments in WGS technology have revealed that most *C. difficile* strains found in humans, animals, food, and the environment are genetically similar and in certain instances, identical. This raises the possibility of zoonotic transmission between people and animals using contaminated food and the environment as a route (Knight et al. 2017; Janezic et al. 2018).

Virulence Factors and Toxico-kinetics of *C. difficile*

There are many virulence factors of *C. difficile* such as its potent toxins, surface-layer protein, spores, and adherence. The two main enterotoxins of *C. difficile's*, tcdA and tcdB (Rupnik et al. 2009), are responsible for its virulence, described by the breakdown of the enterocytic actin-skeleton caused by the Rho-metabolic process. Toxins A and B are prototypical members of the large clostridial cytotoxins (LCT) family and bind to an unidentified receptor on the intestinal mucosa via the carboxy-terminal end. This essential adherence might be dependent on capsular and cell-wall components like S-layer adhesions (P36 and P47) or other immunostimulatory flagellar or fibronectin-binding proteins that have been postulated (Pechine et al. 2007). Through the relocation of the center region, the toxin amino terminal is subjected to internal glucosylation of the Rho proteins required for epithelial cell cytoskeleton formation (Janoir 2016). This causes actin filaments to depolymerize, resulting in the loss of their interior structure, rounding of cells, and breakage of adherent's junctions that keep cells intact. The Inflammatory response and mucosal epithelium loss aided the deterioration of brush border membranes and the villus accelerates the epithelium's malfunctioning. The main fibrin layers arrange to cover ulceration, which stands out on inflamed necrosis debris, creating a knob-like coalescent pseudomembrane colitis (PMC) visible by endoscopy. Although strains that produce only toxin tcdB and lack a functioning toxin tcdA gene can occasionally induce toxin-mediated diarrhea. However, most clinical isolates contain both toxin A and toxin B genes, leading to synergistic pathological characteristics (Rupnik 2006).

Additionally, certain *C. difficile* strains synthesize a third type of toxin located chromosomally, known as a binary toxin (CDT). This toxin is an actin-specific ADP-ribosyltransferase with a high degree of structural and functional similarity with the ι-toxin from *C. perfringens*. Isolate that is positive for toxins A and B also produced CDT (6-30 % of strains) (Rupnik et al. 2009).

Colonization of Pathogen and Associated Diarrhoea

Antibiotic medication often alters the natural gut microbes, which is the major risk factor for contracting infections with *C. difficile* and *C. difficile*-associated diarrhea (CDAD). Various experimental animal models have shown the involvement of antibiotics therapy in dismantling colonization resistance and CDAD, whereby following the inoculation of normal fecal flora transiently eliminates *C. difficile* and symptoms. The relevance of colonization resistance repair is supported by both in vitro inhibition of *C. difficile* growth while subjected to fecal emulsions from healthy individuals and in vivo, the use of curative nasogastric replenishment of normal intestinal flora in human CDAD (Aas et al. 2003). Asymptomatic transmission of *C. difficile* in healthy individuals in the community is very rare (1-15%), raising concerns about the endogenous origin of *C. difficile* in CDAD. However, current findings have shown that in more than 50% of healthy individuals, a toxin tcdB is present (Iizuka et al. 2004). This suggests that *C. difficile* population is present in less proportion rather than nonexistent in healthy intestinal microflora. On the contrary, the environment could potentially serve as a constant source of infection that is amplified by factors, for instance, medical wards that are highly contaminated. *C. difficile* carriage, either intermittent or persistent, tends to lead to CDAD. This is common whenever patients are hospitalized since 15-21% of individuals are colonized with *C. difficile* colonization and antibiotic therapy stimulates the beginning of CDAD (Kyne et al. 2000). *C. difficile* is spread via infected persons, ambient objects, and medical care staff's hands. While asymptomatic carriers won't experience diarrhea (Bobulsky et al. 2008) and they will help the spores spread throughout the environment (Riggs et al. 2007). Although the colonization of *C. difficile* is the primary risk factor, which is often acquired after hospitalization, there are many other significant associated risk factors, which are highlighted in the diagram (Fig. 1). The use of antibiotics is the most significant risk factor and practically all antibiotics currently available on the market have been associated with CDAD (Johnston et al. 2012).

Cephalosporin, Clindamycin, and Ampicillin are the most frequently mentioned drugs accounting for almost 90% of all precipitating antibiotics in CDAD (Leffler and Lamont 2015). Unsurprisingly, a prolonged antibiotic regimen or multiple antibiotic usages raises the chance of CDAD. Antibiotics with minimal risk, such as tetracyclines, rifampicin, aminoglycosides, trimethoprim and the older generation of quinolones, have little effect on the normal inhabitant anaerobes and are rarely the reason for CDAD. Since the advent of newer generations of quinolones class with enhanced anaerobic activity, there is an increased risk of CDAD after using moxifloxacin, gatifloxacin (Gaynes et al. 2004) and levofloxacin (Khurana et al. 2004). This is further shown by the widespread outbreaks in the United States and

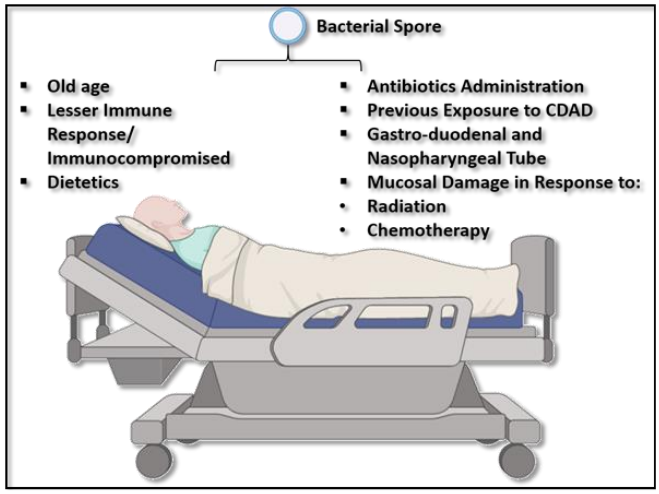

Fig. 1: Possible associated risk factors of *C. difficile*-associated diarrhea (CDAD)

Canada (Loo et al. 2005) caused by increased fluoroquinolone prescription. Effective strategies such as limiting the usage of cephalosporins lower the prevalence of CDAD. In older people ages sixty to ninety, the risk of CDAD increases ten times, as well as other known risks of the host, such as compromised immunity and decreased levels of antibodies against toxin tcdA and tcdB, might further complicate matters (Leffler and Lamont 2015).

Furthermore, a concurrent disease that involves regular hospitalization or an extended stay in the hospital, including many precipitating therapies, such as antineoplastic/ chemo therapy and endotracheal feeding tubes, will result in persistent CDAD (Hung et al. 2013). Using newer proton pump inhibitors (PPI) or laxatives has been linked to an increased risk of CDAD to some extent (Dial et al. 2004). It has been suggested that dietary risk factors for CDAD include starvation after surgery or a diet lacking in non-essential amino acids like proline and cysteine. However, these conditions must be thoroughly investigated in actual clinical settings (Johnston et al. 2012).

Clinical Manifestation of CDAD

CDAD is triggered by alteration in the intestinal flora, a high proportion of toxin-producing *C. difficile*, nutritional imbalance, a compromised host immune system and other variables that regulate toxin release. The interaction of these factors influences the onset of diarrhea, which is commonly defined as a minimum of three loose faeces/ day and represents a self-limiting sickness. CDI's clinical manifestations are quite diverse and may vary from the asymptomatic carrier status, mild to severe diarrhoea, to a life-threatening condition, fulminant colitis. The incubation period is not well defined and some publications imply that it lasts for two to three days. The most recent research has shown that it may last much prolonged than that and varies from person to person (McDonald et al. 2018). CDI may damage any section of the colon, but it is typically seen in the proximal portion. The majority of patients infected with CDI have moderate diarrhea and recover on their own after a week of antibiotic withdrawal. Diarrhea develops in the majority of cases either during or immediately post-antibiotic medication, while CDI may develop days later. Along with watery diarrhea, CDI's clinical manifestations include pyrexia, nausea, vomiting, fatigue, and anorexia. Despite the rarity of actual bleeding, stool testing for blood are frequently positive (McDonald et al. 2018). The signs and symptoms of extreme clinical manifestation of CDI are all potentially fatal such as severe dehydration, abdominal distention, hypo-albuminemia with edema and eventually vascular shock. Extremely sick individuals may seem to be improving clinically by resolving diarrhoea; however, this is typically a symptom of ileus with the appearance of toxic megacolon. Aside from the signs mentioned before, other serious CDI adverse effects include paralysis of the intestine, colonic perforations, renal failure, systemic inflammatory response syndrome (SIRS), septicemia, and ultimately death (McDonald et al. 2018). Despite life-saving surgical treatment, oral medication has less impact at this point, and the death rate has increased to 25–40%. Outside the colon, the clinical manifestation of CDI are uncommon and often include small intestine invasion, reactive arthritis, and bacteremia. Because severe concurrent illnesses might complicate the assessments, it can be challenging to estimate the mortality rate in CDAD (Dendukuri et al. 2005).

Mortality related to CDI complications is about 15–25% and may reach up to 34% in critical care units (CCU); while on the other hand mortality rate directly linked with CDI is estimated to be 5%. When comparing CCU patients with and without CDI, mortality rates increase twofold (Sidler et al. 2014; Czepiel et al. 2015). The poor prognosis is linked to old age, high leukocytosis, hypo-albuminemia, and elevated levels of creatinine (Vaishnavi 2010). Moreover, it has been demonstrated that the first CDI clinical episode raises the overall probability of fatality. Reoccurrence of signs and symptoms of CDI usually appears within the first week following the initial infection, after therapy is completed. Following successful antibiotic therapy of the initial CDI illness, at least one subsequent recurrent disease happens in 10-25% of patients and also occurs in more than 65% of affected patients who have undergone more than one recurrence of CDI (McFarland et al. 1999). According to data, 50% of recurring infections are caused by relapsing of the primary strain, while the remaining 50% are caused by re-infection with other strains. Recurrences are considered to be caused by a compromised host immune system to A and B toxins, along with exposure to spores. Drug resistance seems to have little effect on the likelihood of recurrence (Vaishnavi 2010; Moore 2018).

Diagnosis

Whenever diarrhea symptoms appear (loose faeces more than three times/ day), CDI must be considered immediately. CDI is diagnosed by detecting *C. difficile* toxins (tcdA, tcdB) directly from a faecal sample, most often using an enzyme immunoassay (EIA) that offers a quick turnaround (less than 2 hours) with a sensitivity of 75-85% and specificity of almost 95-100%. It is one of the most widely used assay used in laboratory settings because it is less expensive and easy to use. Antigenic tests for diagnosing *C. difficile* is found mainly on detecting glutamate dehydrogenase (GDH). They are distinguished by their convenience of use, quick response time, and high specificity of about 100%. The only drawback is the low specificity (59%). It fails to differentiate between the strain's toxigenicity and non-toxicity (Bartlett 2010; Simor 2010). In 2009 nucleic acid amplification test (NAAT) was introduced. These tests use the amplification of nucleic acid based on either PCR technique or isothermal amplification. Compared to EIA, NAAT has higher sensitivity and specificity.in case of a negative result, the specificity increases significantly and reaches 95% (Su et al. 2013; McDonald et al. 2018). The NAAT also has certain disadvantages, including significant expense and result in interpretation challenges. The expression of a toxin-encoding gene is confirmed by PCR, which also verifies the existence of a toxigenic strain of *C. difficile*. However, this doesn't certainly imply that the strain is currently synthesizing any toxins. If the diarrhoea is caused by anything else, detecting this strain would be deceptive since it results in additional medication for CDI. Cytotoxic assay tests (CYTA) are not often employed in microbial cultivation because these are laborious and time-consuming with response time of 48 to 72 hours (Leffler and Lamont 2015). The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends no test is available solely for the confirmation of CDI. Combining two assays in an algorithmic approach is the most effective technique for the optimization of CDI diagnosis. The initial test needs to be one with a higher negative predictive accuracy (NAAT or GDH) and the following test should have a higher positive predictive value (EIA). If the initial test result is negative, CDI is ruled out. EIAs should be carried out if the results are positive. CDI is confirmed when the subsequent test results are positive (McDonald et al. 2018). Fig. 2 illustrates the schematic flow sheet for CDI diagnosis.

But if the second test comes out negative, the situation must be reviewed clinically. This may be seen in 3 scenarios: (1) a low level of toxin (below the threshold limit), remains undetected, (2) a false-negative result of EIA (3) carrier of *C. difficile*. Retesting is necessary for samples showing a negative result for GDH but positive for toxin since it's an invalid result (Crobach et al. 2016).

CDI in Animals Interface a Potential One-Health Threat

One Health is a collaborative approach emphasizing that our health and well-being are inextricably linked to animal health and the environment. A key aspect of the One Health initiative, generally and especially for CDI prevention, expanded the collaboration between doctors, veterinarians, farmers, and legislators to improve surveillance and monitoring, research, and establish integrated national policies. For a long time, doctors and vets used non-divergent approaches to treat CDI (Gerding et al. 2008). Public health workers still consider CDI to be solely a hospital-acquired problem and are usually ignorant of the frequency of toxin-producing *C. difficile* in our environment, its One Health implications, such as the fact that *C. difficile*-related death in newborn pigs may exceed 50%, with huge economic ramifications for industries. (Songer and Uzal 2005). Despite previously thought to be a hospital-acquired illness spread from One infected individual to another, Eyre et al. (2013) conducted a study to investigate the intrinsic genetic epidemiology of CDI. The researchers employed highly sophisticated techniques like WGS and core-genome single nucleotide variant (cgSNV) analysis. They analyzed *C. difficile* isolates from 957 hospital- and community-based CDI patients that have been gathered during 2008 and 2011 from UK and discovered that just 35% of isolates were genomically connected to at least one prior case while 45% of isolates were genomically unique from all preceding cases. About 126 out of 333 isolates with an indication of clonal transmission had frequent hospital interaction with some other patient, and 120 isolates had no conceivable epidemiologic relationship with another patient in the healthcare setting or the community. It was proposed that, in contrast to infected patients, other environmental reservoirs potentially have a significant unreported involvement in *C. difficile* dissemination.

According to recent investigations by Sheth et al. (2019) and Halstead et al. (2019), compelling evidence for asymptomatic patients have an important role in CDI transmission in healthcare facilities. In these investigations, asymptomatic individuals were tested for *C. difficile* upon hospitalization, and the resultant isolates were subsequently subjected to WGS and contrasted with isolates from symptomatic CDI individuals using other available techniques like MLVA or cgSNV analysis. About 10-15% of those tested subjects were asymptomatic *C. difficile* carriers, with >80% colonized by toxin-producing strains that can cause illness. These investigations provided evidence for the hypothesis that asymptomatic carriers were spreading *C. difficile* to vulnerable hospitalized patients by transferring the infection from asymptomatically infected persons to patients that are previously negative for *C. difficile* and by grouping asymptomatic individuals with symptomatic CDI patients. Likewise, further different research by Gonzalez-Orta and

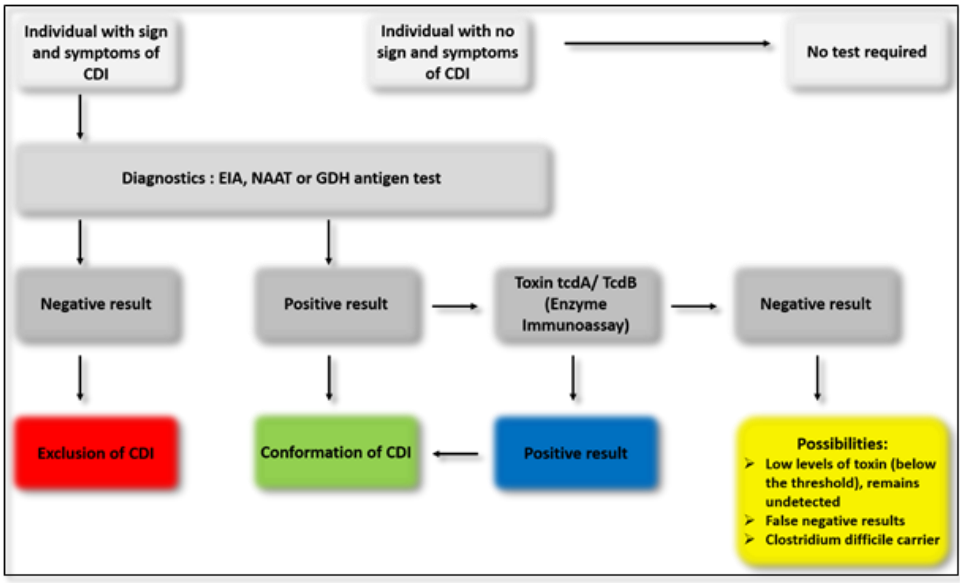

Fig. 2: Flow sheet for the diagnosis of CDI.

associates in the USA demonstrated that nearly 25% of hospital-related CDI cases were diagnosed with strains that the patients had already been colonized at the time of hospitalization (Jencson et al. 2019). This implies that there weren't healthcare facility cases and CDI acquired in the community, with the illness only after hospitalization. With the continuing importation of *C. difficile* strains into the healthcare setting through asymptomatic carriers, community sources/reservoirs may be having a significantly larger role in the transmission of CDI than previously assumed, and the frequency of CA-CDI may have been substantially misrepresented underneath the established categorization rules. Up till now, *C. difficile* is isolated from a wide range of reservoirs/sources such as human-animal (Food animals, seafood, and meat) and environment (natural and household environment) interface (Knight and Riley 2019). The environment (natural and household) and consumable foodstuff (retail food and food animals) are all significant *C. difficile* reservoirs. The infection rates in the newborn are typically high, up to 70% in piglets, and vary between 15-20% in calves. A higher prevalence (42%) of *C. difficile* was reported in the United States (DePestel and Aronoff 2013). On the other hand, findings from a European study, point out a far lesser number (only 3%), maybe because of different slaughtering management practices (Candel-Perez et al. 2019). *C. difficile* is also often found in natural settings including water and soil where its incidence ranges from 30 to 50 %. In these investigations, the most prevalent strain was *C. difficile* RT 014 belongs to MLST cluster 1 (ST2, ST13, and ST49) and cluster 5 (ST11 RTs 33, 78, 126, and 127). In humans, CDI is associated with the lineage RT 014 and ST11 (Knight and Riley 2019). Both possess wide genomes and consistently evade the effects of many antimicrobials being used in human and veterinary practices (Knight et al. 2017; Knight et al. 2019). Thus, this again emphasizes how *C. difficile* is relevant to the concept of One Health, which states that three separate issues need an integrated solution i.e., human-animal health and the environment. Currently, no concrete evidence exists that *C. difficile* is transmitted via faeco-oral or the environmental route. This evidence is hard to get because (1) not every person exposed to *C. difficile* exhibits signs and symptoms (depending on the susceptibility of their gut microbiota), (2) *C. difficile* is widespread, and (3) the sporulation capability of *C. difficile* (spores can stay quiescent till the favourable environment for the propagation). Furthermore, the infectious dosage (ID_{50}) for CDI in the human population is uncertain. Nonetheless, thanks to the advancement in microbial genetics, presently there is sufficient and persuasive proof that *C. difficile* endemic to humans and farm animals has a contemporary evolutionary history, and also that CDI has a significant zoonotic element, resulting in contamination of consumer food and the environment. Based on an investigation by Knetsch et al. (2018), the results of core genome analysis showed considerable clustering of human and animal strains, indicating that *C. difficile* may transmit both ways between farm animals and humans. A clonal cluster RT 078 revealed transcontinental transfer between an animal in Canada and humans in the United Kingdom. Tetracycline is extensively employed in veterinary medicine. In a study by Dingle KE et al. (2019), tetracycline preference was recognized as an essential driving factor for the evolution of *C. difficile* RT 078, with various tetM-related clonal expansions happening in early 2000. An agrarian perspective for *C. difficile* RT 078 is even further supported by the emergence of various tetM components, which are Tn916-like components from proven zoonotic pathogens such as *E. coli*, *E. faecalis*, and *S. suis*. In Australia, *C.*

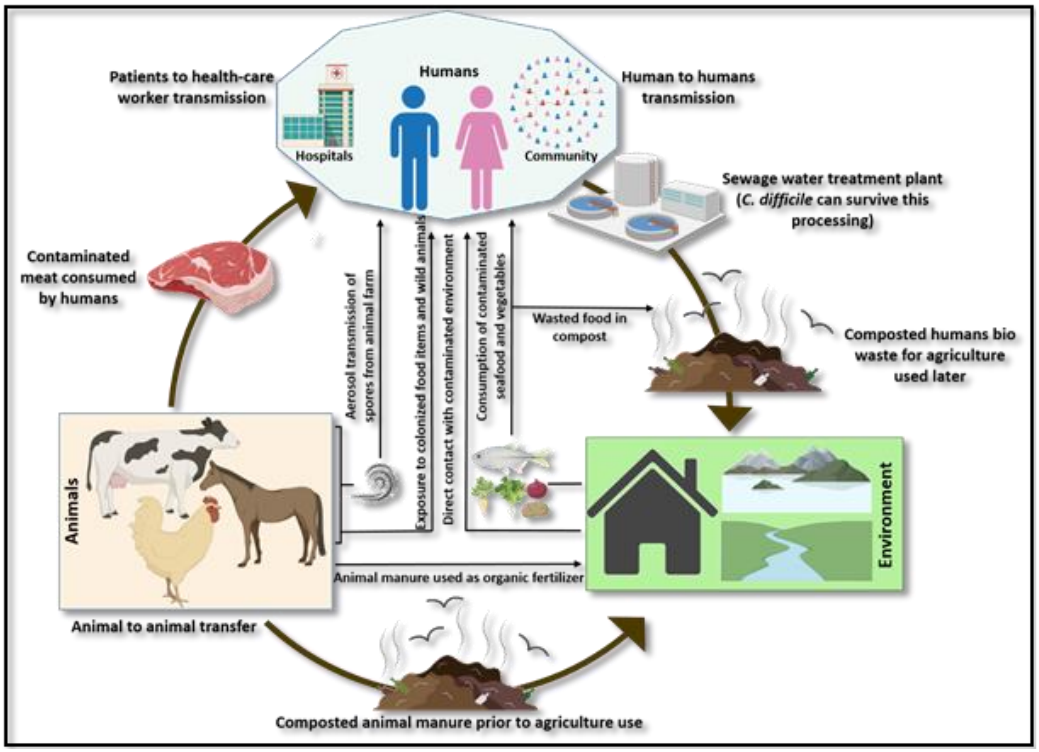

Fig. 3: Transmission cycle of *Clostridium difficile.*

difficile RT 014 is very common in humans and pigs with CDI, accounting for about 30% and 25% of isolates, respectively (Knight et al. 2015; Collins et al. 2017). A researcher (Knight et al. 2017) isolated and sequenced the collection of the RT 014 strain of *C. difficile* from humans and pigs at the same time. The results of the cgSNV analysis showed current cross-species transmission, with 42% of strains isolated from humans sharing a clonal connection with at least one animal isolate. Furthermore, it is doubtful that there's any direct interaction between both humans and animals since these clones were isolated hundreds of miles away throughout several Australian states. By considering all the facts it seems that *C. difficile* strains often circulate between people and farmed animals and that the zoonotic transmission is not restricted to any specific territory or the general populace. This clearly explains an inter-linked long-distance zoonotic transmission mechanism including potentially contaminated foodstuff and/or extensive dispersion of *C. difficile* in the environment. Indeed, research has demonstrated that RT 014 and other clinically significant and quite often antibiotic-resistant *C. difficile* lineages are found in retail food, waste, outdoor parks, domestic environments, and domesticated animals (Knight and Riley 2019). Now there raised a question that how this transfer of *C. difficile* between humans and food animals is possible with limited geographical clustering. Humans and animals both are the primary hosts for *C. difficile*. Since its spores can withstand the required cooking temperature for meat (71oC) for more than 2 hours, *C. difficile* from farmed animals may contaminate meat throughout the slaughtering procedure and survive until consumed by us (Rodriguez-Palacios et al. 2010). *C. difficile* spores may also spread via aerosols, as seen in hospitals and surrounding animal farm facilities. Based on regional agronomic systems and regulations, manure from livestock may be composted or used as organic fertilizer that is dumped directly into agriculture farms which might lead to contamination of the agricultural environment. It's doubtful that *C. difficile* spores will be eliminated from the manure, even after composting. Two-thirds of the composting material including mulches and soil mixture is still contaminated with *C. difficile* (Perumalsamy et al. 2019). Additionally, it is possible to compost contaminated food waste for later use in landscape and horticulture. Fig. 3 illustrates the important CDI reservoirs and potential transmission pathways.

When treated sewage is released, it may harm surrounding streams, lakes and rivers, and seafood (Troiano et al. 2015) because *C. difficile* can withstand the sewage treatment (Romano et al. 2012). There have been reports of direct zoonotic transmission of *C. difficile* between pigs and their farmer (Knetsch et al. 2011); nevertheless, for the public at large, indirect zoonotic dissemination via foodstuff and the environment seems to be more probable. Because *C. difficile* is so extensively spread in the population, residential settings and domestic pets are being colonized with *C. difficile*, opening up yet another pathway for transmitting CDI (Orden et al. 2018).

Conclusion

Treatment options for CDI have been limited to metronidazole and vancomycin since the late 1970s, when *C. difficile* was first identified as the causative agent. Consequences of CDI go far beyond gastrointestinal symptoms and are often overlooked. Recognizing the potential psychological and social effects of CDI and identifying payment assistance programmes, supportive services, and work medical leave options are all important parts of clinical treatment and management, but they are only part of a holistic approach that must take into account not only pharmaceutical intervention but the patient's experience both during and after CDI. Health resources and healthcare institutions should focus on avoiding CDI and CA-CDI to cut down on expenditures on medical treatments.

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