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Campylobacteriosis in humans & poultry and sustainable rescue options

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ABSTRACT

Campylobacter jejuni constitutes the front runner bacterium towards causing gastroenteritis globally. It is usually contracted through consuming improperly processed poultry products and by intake of contaminated water. Post intake, the bacterium tends to adsorb or attached to the gut epithelial lining and incites toxin-associated deferment of liquid re-absorption from the gut plus invasive inflammatory manifestation along with diarrhoea. Acute or chronic or persistent campylobacteriosis are dealt with antibiotics and proton-pump inhibitors. However, an ever increasing problem of antibiotic resistance evolution has been there and that is alarming. Thus, urgency exists for finding out non-classical therapies as reduction factors against *Campylobacter* nuisance in humans and poultry. In addition, a few probiotics have been instrumental to cut down the adverse effects rendered due to the classical antibiotic therapies with particular reference (wpr) to GIT. Particular probiotic strains (including *Lactobacillus johnsonni* La1 and *Saccharomyces boulardii*) have been able to downgrade the concentration of bacteria. It has been reported that *Lactobacillus reuteri* is at par in efficacy in this regard. The aim of this article involves the provision of an update of the present and futuristic approaches and therapeutics to eradicate infections in animals and humans. Miscellaneous approaches include anti-*Campylobacter* compounds, probiotics, bacterial viruses, and vaccination and bacteriocins. These approaches have shown successful results towards lowering the occurrence of *Campylobacter*-associated ailments in humans and for bioclustering in the poultry houses and animals.

Keywords: *Campylobacter,* Bioclustering, Food safety, Resistance evolution, Probiotics, Toxic/Side effects

INTRODUCTION

Campylobacter jejuni causes the gastrointestinal inflammatory process. This bacterium is indeed heads the world-wide based sources of this ailment. Campylobacteriosis has been prevalent in endemic form in especially young children Africa, Asia and Middle East, while there is a considerable rush up of incidence and occurrence in continents covering North America, Europe and Australia (Kaakoush et al., 2014a). Burden of treatment cost of acute infection and thereafter complications are colossal in countries like USA. The microbe after being ingested tends to adhere and follows invasion of cellular epithelial linings of the GIT to excite hostile inflammatory events. The sequence ends up in bearable or disturbing diarrhoeal condition (along with bloody stool, cramped abdomen and pyrexia). In some cases gastroenteritis may enter in septicemic and arthritis like complications and syndromes (like Guillain-Barré syndrome and Miller Fisher), IBD (inflammatory bowel disease) e.g. Crohn's syndrome and UC (ulcerative colitis) (Backert and Hofreuter, 2013; Maue et al., 2014; Kaakoush et al., 2014b; Goldstein et al., 2016).

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It appears *Campylobacter* relevant diseases exert a sizeable pressure in the countries that are under development. However, infections remain in self-limiting category in the immuno-normal patients of developed countries, but infection continues to disturb the young children and possibility of stunting remains as an alert. *Campylobacter* bacteremia causes chronic diarrhoea in AIDS patients, where mortality-morbidity trends show an increase in the developing world (Coker et al., 2002; Guerry et al., 2012; Amour et al., 2016). *C. jejuni* leadingly causes food-related diseases because of symptomless colonization in agro-animals inclusive of poultry birds (in advanced countries) (Johnson et al., 2015). Actually, poultry birds undergo life-long natural bioclustering within 14-21 days after being hatched through horizontal contamination from ecosystem. Even domestic or indoor and wild type birds become the initial reservoir and can further spread from poultry gut to meat (during processing steps) (Sahin et al., 2003; Meunier et al., 2016b).

Sizeable source of human Campylobacteriosis is attributed to poultry birds and this link can be discouraged by proper defying of the avian colonization. This strategy has been worked out as a shortfall of *Campylobacter* bioclustering of poultry birds by 2-$\log_{10}$ that may lower down the human infections by 30-fold (an approach that could have tremendous impact on health of the humans (Rosenquist et al., 2003). Contaminated chickens are reported as the leading mode of diseases in developed world while contaminated water is generally considered the cause of *Campylobacter* infections in developing areas of the globe (Kaakoush et al., 2015). As such, the disease is self-cured. It is often suggested that antibiotic treatment options should be discouraged. However, in persistent and serious cases like immuno-compromised individuals, Campylobacteriosis may be prescribed with macrolides (erythromycin) or quinolones (ciprofloxacin) antibiotics (Kovaˇc et al., 2015). Then, the million question remains to be responded as to opt for the novel parallel options to combat the drug resistant strains (Kumar et al., 2016). According to Centre for Disease Control and Prevention (CDC, USA), the resistance to ciprofloxacin showed an increased trend for 13 to 25% between 1997 and 2011 (Hampton, 2013). It is noteworthy that global travel-assisted *Campylobacter* infections in the US are caused by the quinolones-resistant *Campylobacter* and manifested 60% of antibiotic resistance and it is of interest to compare this with 13% resistant *Campylobacter* of non-travel associated cases (Ricotta et al., 2014). The financial burden laced with *Campylobacter* infection and post infection syndromes seem colossal and this warrants new intervening approaches for reducing the colonization incidence in commercial chickens and human Campylobacteriosis. Thus, optional therapies and potential targets search for futuristic researches may provide guideline to develop anti-*Campylobacter* therapies (Pearlin et al., 2020).

Sources and Bioaccumulations of *Campylobacter*

Campylobacter is ubiquitous in varied wild and domestic animals. In fact, birds constitute the basic housing of *Campylobacter* spp., however, grossly putting without symptoms (in lower GIT of animals) (Weis et al., 2016). As such warm blooded (40^{o}-42^{o}C) birds offer a congenial ecosystem of *Campylobacter* growing in poultry inclusive of chicken and turkey. Hence, they can be isolated from these birds in addition to miscellaneous household and wild birds such as crows, ducks, quail and even starlings. The microbe even inhabits livestock (Cattle, goats, cows, pigs, sheep etc.) (Manyi-Loh et al., 2016; Hamrita and Conway, 2017). Wide presence of *Campylobacter* is a contributing cause of the food to man transmission particularly the excessive prevalence of agro contaminants in the ecosystem (Fig. 1). As such, *Campylobacter* may inhabit among wide range of animals, it is not beyond reason to believe that certain strains show their preference for some hosts. This notion would enable the epidemiological studies of the sources of infection. Thus, Weis et al. (2016) were able to compare *Campylobacter* strains (isolated for humans, chickens, cows, crows, goats and sheep). Accordingly, 17% of *Campylobacter* spp. from crows showed appreciable similarity with the ones from humans, primates and sheep, thereby pointing that multi-genotypes are harbored within individual *Campylobacter* spp. In case of *C. jejuni*, a proof could be offered for adaptation viz a viz host species. The study of diversity-based strains may offer prospective targets for further investigations leading to intervening strategies to block the spread and continued presence in animal settings (Abd El-Hamid et al., 2019).

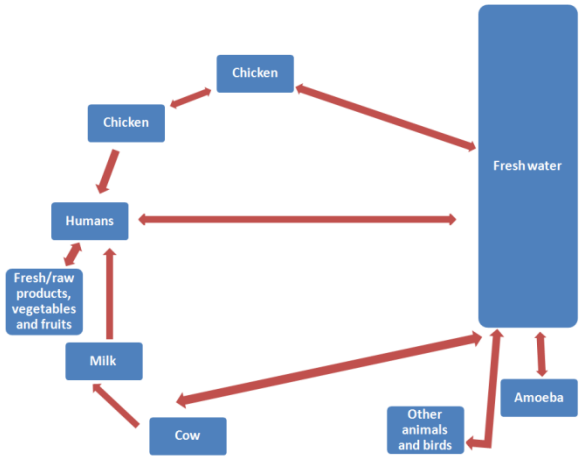

Fig. 1: Various sources, reservoirs and transmission of *Campylobacter*

Biofilm forming capacity of *Campylobacter* spp. is an awful factor for their continued presence in the environment. The biofilms are formed as a variety of inanimate areas e.g. channels for water supply (Duarte et al., 2016). Actually, biofilm help microbial entities to live in such ecosystems that in normal circumstances may fail to entertain. This activity facilitates their access to sufficient nutrients in addition to providing safe heavens where these species remain inaccessible to bioactive molecules such as water added disinfectants. This biofilm formation scenario allows these microbes to sustain and live in water for 3 weeks or so (Lehtola et al., 2006). An interesting factor that works for the biofilm formation constitutes "Quorum sensing" (QS) which is a cell to cell communication system associating the formation and manifestation of excretory communication molecules. In fact, QS signal practices are webbed to bacterial preoperative activity in food-feed spoilage. Thus QS deferring constitutes a good goal to avert *Campylobacter* (for food security purpose). Further, biofilm enhances the capacity that confers *Campylobacter* resistance to drug capacitated by gene trafficking by horizontal mode. All this narrative equates to the research capacity for targeting biofilm manufacturing and the responsible genes transfer among *Campylobacter* populations (Nazzaro et al., 2013; Zhong et al., 2020).

Genetic factors that determine *Campylobacter* resistance to drugs

The urgency for non-classical antibacterial approaches to cut down *Campylobacter* in poultry (and products) is obvious. This approach is in line with the aim to cut down the human health and financial pressure encountered by drug-resistant *Campylobacter* disease. Multi-target approaches (e.g. evolution of anti-*Campylobacter* remedies by targeting themselves) or through permitting the evolution of approaches circumventing the ways out of resistance. Antibiotic resistance by *Campylobacter* is acquired either by mutations of spontaneous type or by in vivo gene transfer processes (conjugation, transduction and transformation) (Duarte et al., 2016). Presence of *tet* gene on conjugative plasmids plays considerable part to spread tetracycline resistance (wpr to *Campylobacter*) (Pérez-Boto et al., 2014). *CmeABC* is the very well researched antibiotic resistance factor. It is an energy reliant multiple drug efflux pump and in case when this pump inhibitor carbonyl cyanide in chlorophenyl-hydrozone (cccP) was added to *C. jejuni*, growing cell, a quick and considerable enhancement in ciprofloxacin cell binding occurred (Oh and Jeon, 2015; Lin et al., 2002). *CmeABC* constitutes 3 constituent proteins i.e. the fusion periplasm located (*CmeA*) protein, the inner membrane drug transports (*CmeB*) and *CmeC* (an OMP). Resultantly, a *cmeB* mutant of *C. jejuni* 21190 was found more sensitive to drugs. *Campylobacter* drug resistance is also related to mutation in the DNA gyrase subunit A (*gyrA*) (Kovaˇc et al., 2015; Kumar et al., 2016). Phenolic compounds have even be suggested for developing the "antimicrobial adjuvants", these could defer the function of resistant genetic determinants and consequently lowering the capacity of these bacteria to sustain the antibiotic presence. This could strengthen the function of existing drugs. Phenolics could also be suggested as diet supplements while treating the Campylobacteriosis with antibiotics (Oh and Jeon, 2015).

Considerable number of *C. jejuni* strains undergo mutations and exhibit broad genetic diversity and that accelerates the frequency of drug resistance and virulence in *Campylobacter* (Young et al., 2007). According to Bae et al., (2014) strains of this bacterium having developed antibiotic resistance (genetic factors); the some may be transferred to planktons (cultures) in addition to their bio-tilting in biofilms. A mere interesting feature lies in the fact that *C. jejuni* than from elsewhere (Wang and Taylor, 1990). We understand the frequency of transformation efficiency goes along the enhanced bacterial concentration (that perhaps provides ample extraneous DNA in bacterial cultures (Wilson et al., 2003). Further, limited oxygen tension offers a congenial for enhanced free DNA intake (as may be the condition prevailing in GIT). So GIT evidently regulate the environment guided in vivo horizontal trafficking of gene(s)

(Young et al., 2007; Sabino et al., 2019). Thus, one thing seems obvious that intervening mechanisms should well be worked out to check in vivo transformation in *Campylobacter*.

Counter *Campylobacter* Compounds

A logical approach lies in developing the compounds that may antagonize *Campylobacter* in agriculture. These molecules may be exploited against the pathways which contribute to clustering or can serve as narrow spectral inhibitors of *Campylobacter* growth. However, such molecules and compounds should differ from those prescribed as human medications. Examples include the small molecules which defer flagellar expression. Johnson et al., (2015) conducted such a study in which 147, 000 low molecular weight molecules that could interfere the flagella movement and of cause other "Campynexins" compounds which could arrest only *Campylobacter* strains and not *Helicobacter pylori* growth in vitro (<10µM or ICS50s). The inhibitory show up was not hostile to GIT-based microbes. Kumar et al., (2016) revealed that these compounds with low toxicity are anti-cells. Low level of compounds are bacteriostatic or bactericidal at 200µM concentration for *Campylobacter*. These are non-hemolytic for sheep RBCs. These compounds represent aryl amines, piperazines, pyridiazinones, sulfonamides and piperdines. The chicken with *Campylobacter* colonization may be treated with the above referred bioactive molecules. The research by Johnson et al. (2015) is appreciable who worked on one day hatched chicks (to gauge the effect of Campynexin wpr to GI colonized scenario). Similarly, these bioactive molecules may be used for in vivo investigations for their potential as anti-*Campylobacter* for treating the human Campylobacteriosis (Johnson et al., 2017). In this view, these bioactive molecules may be used as feed or aqua additives. However, the concerns have been shown regarding the wide-spreading of such synthetic molecules to the meat that reaches out the consumers. Hence, natural additives may be developed to address these concerns (Navarro et al., 2015). It may be mentioned that plant derived phenolic compounds carry counter *Campylobacter* bioactivity (Klanènik et al., 2012). According to this study, the *cmeB* gene mutated inactivity leads *Campylobacter* considerably sensitive to phenolic compounds; this is suggestive of the understanding that transportation (from intracellular compartments) of such compounds is needed for conferring the resistance. Some anti-*Campylobacter* compounds, their effects and mechanisms of action are listed in Table. I. According to Navarro et al. (2015), a long listed plant origin extracts (basil, campasicum, bark of cinnamon, garlic, clove, laurel, lemon (and grass), lemon myrtle, mandarin, sweet and bitter orange, rosemary, thyme and sage) have shown anti-*Campylobacter* activity. This study also revealed that essential organic oils (MIC being 0.0038%) carry potential activity against *Campylobacter* (formic acid tops the list). Similarly, garlic and organo-sulfur compounds also harbor considerable higher levels of antibacterial bioactivity as compared to phenolics. Amazingly, antibacterial activity of garlic derived organo-sulfur compounds did increase concomitant to the enhanced sulphur atom number (Lu et al., 2011). Still, Pogaˇcar et al. (2015) showed that natural compounds (thyme ethanol extract, thyme post-hydro re-distillation residue) were able to downgrade adherence potential of *C. jejuni* to pig epithelial cells of small intestine. The practice of such and similar strategies may help decrease the feed-diet formulations. Cheaper deferring agents (safe as well) should be an attractive approach to knock out the evolution of drug resistant bacterial species. Such an approach may prove helpful to mitigate colonization in poultry sector and treatment of human *Campylobacter* disease (Micciche *et al*., 2019).

Table. I Anti-*Campylobacter* compounds and their mode of action

Anti-*Campylobacter* Agents	**Mode of action**	**References**
Campynexins	*Campylobacter* growth inhibitor	Johnson et al., 2015
Thyme	Avoid *Campylobacter* adherence to epithelial cells of small intestine	Pogaˇcar et al., 2015
Ajoene (Organosulfur)	Sulfhydryl-dependent *Campylobacter jejuni* enzyme inhibitor	Rehman and Mairaj, 2013
Resveratrol (Phenolic compound)	Efflux pump inhibitor	Klancnik, et al., 2017
(4R)-(-)-carvone (Terpene)	Cell membrane dysfunction	De Carvalho and Da Fonseca, 2006
Amentoflavone, Carvacrol	Inhibition of adhesion during	Klančnik et al., 2018,

	biofilm formation	Wagle et al., 2019
Carvacrol	Reduction in biofilm formation	Wagle et al., 2019
Resveratrol	Inhibition of biofilm formation	Duarte et al., 2015
Carvacrol	Interference with flagella function	van Alphen et al., 2012
Formic acid	Prevents colonization and kills *Campylobacter jejuni*	Peh et al., 2020

Campylobacter may be rescued by probiotics

There is no denying for the marvelous role of gut microbiome in lowering down the prevalence of *Campylobacter* associated infections in host animals (with antibiosis mode). This practice has become considerably popular (also that this may be instrumental to lower down the incidental occurrence of the drug resistant as such antimicrobials are not needed herein) (Kemmett, 2015).

So far, counter-*Campylobacter* treatment using probiotics has produced considerably satisfactory results. Many of these studies have emphasized on deferring the colonization of *Campylobacter* (mediated by probiotics) in broiler chickens by competitive knockout of the pathogen. Competition based knockout modes constitute the capturing of adhesion receptocytes, excretion of bio active microbial metabolites and struggle of common nutrients. Such application may help lower down the burden of *Campylobacter* in commercial poultry products and ultimately for safe human consumption (thus deferring campylobacteriosis prevalence). After all, probiotics may also be exploited as prophylactic for trend-associated case of campylobacteriosis or for the treatment of campylobacteriosis persistence in endemic areas (Fanelli et al., 2015; Thomrongsuwannakij et al, 2016). Probiotic organisms that are frequently tested for reducing *C. jejuni* clustering include *Lactobacillus* spp., *Bacillus* spp. and *Enterococcus* spp. (all these are residents of animal gut). In addition, *Bifidobacterium* spp., and *S. cerevisiae* have also been exploited for the same purpose (Fanelli et al., 2015; Thomrongsawannakij et al., 2016). According to Thmrongswrannkij et al. (2016), *L. acidophilus*, *B. subtilis* and *E. faecium* were orally administered to broiler chickens followed by a challenge with *C. jejuni* but found insignificant decrease in *Campylobacter* count when compared with control chickens. However, Wine et al., (2009) revealed that *L. helveticus* R005 did lower *C. jejuni* strains invasion of T84 cells to the extent of 41-35%. In another study (Arsi et al., 2015a), 117 bacterial strains harboured in ceca of broiler chicken, were subjected to screening and only 3 species could confidently lower *Campylobacter* clustering in chicken. Significantly, findings revealed that mixed Lactobacillus strains could defer the growth of *C. jejuni* (in vitro), probably because of production of organic acid by the mixed cultures (Bratz et al., 2015). In fact, these Lactobacilli reduce pH for confronting themselves as an effect contributed by multiple strains (Wang et al., 2014; Wooten et al., 2016). However, this pH lowering approach may not be suitable in vivo as such the large intestine is amply buffered by the bicarbonate of pancreatic secretions. According to Arsi et al. (2015b), the load of *C. jejuni* was lowered in vivo to the extent of 1-2 $\log_{10}$, instrumented by 6 strains of *Bacillus* spp. out of a total of 116 bacteria that were isolated and screened. These findings are suggestive that it is effective to administer the broiler breed birds intra-cloacally with probiotic strains. This practice could also defer the requirement for encapsulation of the probiont. However, such an approach seemingly may not go well while keeping the labor cost in mind as such intra-cloacal inoculation of huge number of birds warrants excessive exercise.

Prebiotics did show an appreciable lowering down the load of *Campylobacter* while applying in combo with 3 probiotic spp. (Arsi et al., 2015a). While supporting this study, Gracia et al. (2016) found that reduction in *Campylobacter* concentration was possible with a mix of probiotics and prebiotics. *Saccharomyces cerevisiae* may even exert deferring capacity against *Campylobacter*. Accordingly, *S. cerevisiae* (as supplement) lowered the load of Salmonella and *Campylobacter* in the fecal material, cecum, skin of breast and neck of chickens. This antagonistic show was however impressive in that *S. cerevisiae* enhanced the growth of Lactobacilli (that through nutrients and intestinal receptor adsorption based competition inhibited the two pathogens). Some elements of inconclusiveness of these studies may exist in view of the scenario that stimulation of Lactobacillus by *S. cerevisiae* is rather laced with contradiction because their excessive presence in multi ecosystem is frequently related inversely). The more conclusive study is warranted viz a viz to the capacity of *S. cerevisiae*-promoted antagonism of *Campylobacter*.

It may be noted that a number of other advantages are conferred by the probiotics upon their host. Thus, in a study (Stef, 2016), wherein two or more Lactobacillus strains were mixed with feed, the poultry birds manifested an enhancement in metabolism, nutrient channelling efficiency, synthesis of proteins, adaptation and reaction to exogenous stimuli. It seems, the application of probiotics does matter but at occasions in lowering the clustering of *Campylobacter* in poultry chickens. This situation may be related to lapses, encountered in these research studies (Meunier et al., 2016a). The variables imply the selection of varied chicken lines (Humphrey et al., 2014). Further, the variation in *Campylobacter* strains, dosage and choosing variable routes of inoculation and timing may serve to observe lapses (Meunier et al., 2016a). It may also be of interest that, instead of using human gut or cervical lines for investigating counter *Campylobacter* potentials of probiotics the avian cell lines use may be preferred (Saint-Cyr et al., 2016).

It seems worthwhile that probiotic research should be focused to understand whether the probiotic merits and *Campylobacter* countering abilities could be mimicked in the animal set up of human Campylobacteriosis. It is rather cumbersome to undertake such kind of study as such human Campylobacteriosis mimicking animal model system seems questionable (Mohan, 2015). No doubt models of mice (Stahl et al., 2014), rats (Sung et al., 2013) and ferrets (Fox et al., 1987) carry relevance for such research, still in depth research may serve the purpose for understanding their efficiency.

A novel phenolic antimicrobial, Auranta 3001 may decrease the adsorption investigating of gut epithelial cells by 2 type VI secretion system (J6SS) positive poultry isolates (*C. jejuni* RC039 and *C. coli* RC103). This phenolic compound is able to down-regulate the *hcp* and *cetB* genes (having participatory role-T6SS function) expression. Further, the motile activity of both the strains was aggressively reduced (in vitro). The compound can decrease profile of cecum clustering. In fact, this novel phenolic agent lowers the pathogenesis of T6SS *Campylobacter* along with infliction of colonization flaws (in vivo) (Sima et al., 2018). According to another study, 46 Lactobacilli were isolated from poultry birds' fecal material. All could synthesize bioactive metabolites on media along with antimicrobial characteristics against *C. jejuni* and *Campylobacter coli* with *L. reuteri* and *L. salivarius* manifesting amply powerful bioactivity (Dec et al., 2018).

Amplicon sets produced in multiplex PCR (Fig. 2), are shown in two percent agarose (*C. jejuni* and *C. coli* and wildtypes 7, 15, 27, 41) (Dec et al., 2018)

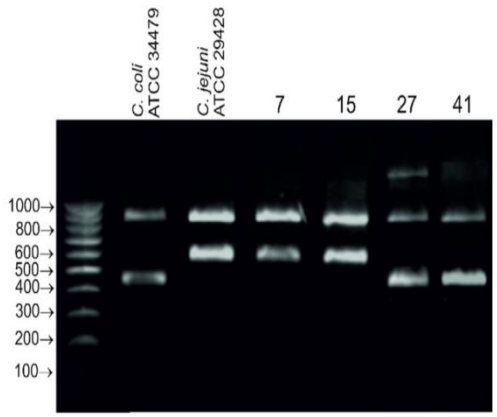

Fig. 2: Amplicon sets produced in multiplex PCR, shown in two percent agarose (*C. jejuni* and *C. coli* and wildtypes 7, 15, 27, 41) (Dec et al., 2018)

In Fig. 2 Dec and colleagues amplified 16S ribosomal gene (860bp), *map*A gene (590bp) specific for membrane associated protein A and *ceu*E (490bp) encoding iron binding transport protein for siderophores in *Campylobacter jejuni* (7 and 15) and *Campylobacter coli* (27 and 41) (Dec et al., 2018).

Vaccines for *Campylobacter*

Vaccination practice in poultry as prophylaxis can prove effective for elimination of *Campylobacter* from birds and incidence reduction of human Campylobacteriosis (inclusive of poultry to human transmission and non-dependency for costly post-harvest measures). *Campylobacter* does not directly affect the poultry health etc., but the cost of the infection to public health (system) and labor output loss is enormous, therefore, vaccine development will help decrease human health risk factors and elevate food security-safety (Avci, 2016; Saxena et al., 2013; Shane, 2000).

In spite of the narrative given in the above para, at present, there seems no vaccine (marketed) to lower the count of *Campylobacter* in GIT of the poultry (Meunier at al., 2016b). Nonetheless, a relevant summarized version regarding the antigens exploited as contenders of *Campylobacter* vaccines (Table. II). Accordingly, ToxC-GT glycoprotein, CjaA, CadF, CmeC, Dsp, total OM proteins, fusion proteins, extra-cytoplasmic proteins, *Campylobacter* flagellin, total cell vaccine-*C. Jejuni* 81-176; protein subunit vaccine and

Campylobacter capsular polysaccharide are worth mentioning (Wyszy´nska et al., 2004; Buckley et al., 2010; Theoret et al., 2012; Riddle and Guerry, 2016; Johnson et al., 2017). A patented vaccine has been in the marked which constitutes a genetically manipulated bacterium to synthesize minimum of one *Campylobacter* derived N-glycan and one acceptable (physiological-based diluent, excipient) adjuvant. The poultry birds treated with patented ToxC-GT glyconjugate carried an appreciable lowering of *Campylobacter* in the inoculated chicken cecum contents. This source vaccine may be produced for inclusion into the livestock feed (Szymanski and Nothaft, 2016; Poly et al., 2019).

According to Wyszy'nska et al. (2004), the chicken immunized with non-virulent Salmonella strains (that exposed CjaA of *Campylobacter*) did appreciably lower the tendency of *C. jejuni* for colonizing the poultry cecum. Similarly, Buckley et al. (2010) revealed that attenuated (live) vaccine de Salmonella (expressive of CjaA *Campylobacter*) proceeded to a reduction of 1.4 log10 CFU/g *C. jejuni* in chicken cecum material. Still another finding by Theoret et al. (2012) revealed the effectiveness of recombinant attenuated *S. enterica* strain that synthesized the Dsp protein (observing a 2.5 log10 lowering of *C. jejuni* in poultry) after challenge. Neal-Neal-Mckinney et al. (2014) assessed number of recombinant *C. jejuni* peptides plus fusion protein as poultry vaccine(s) and found that the maximum decrease in *C. jejuni* clustering in birds inoculated with a recombinant FlaA or FlpA peptide or a fusion CadF-FlaA-FlpA protein. These vaccine versions ended in >2 log10 lowering of *C. jejuni* clustering. Devices for delivery were also analysed. *Campylobacter* flagellin was also assessed as effective immunogenic protein (Meunier et al., 2016b). It appears, immune response against flagellin could not be co-matched with a downing trend in clustering of poultry gut. A fair volume of research has been conducted for the human *Campylobacter* vaccine (for marketing to travellers and other stakeholders). However, the success story is rather dim because the strategy has not been able to confer ample immunity (Maue et al., 2014).

Human subunit *Campylobacter* vaccine has attracted appreciable interest. The total cell oral vaccines have not found preference as vaccine against *Campylobacter* (Riddle and Guerry, 2016). A flagellin subunit vaccine was found marginally immunocompetent in phase 1 testing (Tribble et al., 2008). Schumack et al. (2016) brought a vaccine conjugate against capsule polysaccharide of *Campylobacter*, which absolutely protected diarrhoea from or *C. jejuni* (homologous) strains. Actually, vaccine development is laced with many lumps which need to be cleared. It is cost ineffective process. The stages therein are complex, lengthy and accompanied with economic yet technological odds (Lund and Jensen, 2016). Only a minor portion of all candidate vaccine manufacturing is restricted by unfinished comprehension of their protective epitopes, antigenic diversions, pathogenic potential and their shake-hand with post-infectious syndromes (e.g. IBS, reactive arthritis etc.) (Riddle and Guerry, 2016; Poly et al., 2019).

Table. II The suggestive immunogens based candidate vaccines for Campylobacyteria

Antigen	**References**
ToxC-GT glycoconjugate	Szymanski and Nothaft, 2016
CjaA	Wyszy´nska et al., 2004; Buckley et al., 2010
CadF, FlpA, CmeC, and Dsp	Theoret et al., 2012; Neal-McKinney et al., 2014
ACE 393	Riddle and Guerry, 2016
CPS conjugate vaccine	Riddle and Guerry, 2016
CWC	Poly et al., 2019
rFla-MBP	Poly et al., 2019

Keys: ToxC-GT glycoconjugate= N-glycosylated fusion protein, CjaA= *Campylobacter jejuni* A, CadF, FlpA, CmeC, Dsp= Recmbinant fusion protein, ACE 393= Recombinant protein, CPS= Capsule conjugate vaccine, CWC= *Campylobacter* Whole Cell, rFla-MBP= recombinant Flagellin

Phage therapy against *Campylobacter*

The bacterial viruses are on the focus as therapeutic approach to minimize *Campylobacter* bioclustering in poultry trade. In fact, these host-specific viral entities can be exploited without disturbing the resident microbiome of the poultry at farms and ultimately lowering the *Campylobacter jejuni* entry into the food chain. Hence, these viral particles offer themselves as promising intervention directed *Campylobacter* therapy (El-Shibiny et al., 2009). A number of researches had suggested following this approach (Atterbury et al., 2005; El-Shibiny et al., 2009).

The isolation sources of these lytic bacterial viruses include sewage, pig manure, poultry carcases, broiler chicken etc. (Grajewski et al., 1985; El-Shibiny et al., 2005; Hansen et al., 2007). According to Atterbury et al. (2005), the concentration of *C. jejuni* in broilers was appreciably decreased once phages were present (means of 5.1 log10 CFU/gm phage loaded chicken and 6.9 log10 CFU/g in chicken not harboring phages). Different levels of log_{10} CFU of *Campylobacter* per gram were reported by different investigative outcomes (post phage treatments in different cases) (Connerton et al., 2008; El-Shibiny et al., 2009). Most sought after candidate *Campylobacter* phage is CP220. It has been proposed that a 30 fold decrease in human infections would be potentially possible by the specific phages to exert viable impact. One limitation exist while exercising this phage therapeutic strategy i.e. there is a need to lower down the cut off phage titer of an effective show of rescuing *Campylobacter* count. Otherwise, it appears difficult to address chicken by chicken on mega farms. An important factor lies in the fact that *Campylobacter* is prone to genetic instability and that characteristic may hamper *Campylobacter* from phage onslaught. However, phages also continue evolving themselves to crack down the barriers of the host bacteria (Carrillo et al., 2005; El-Shibiny et al., 2009). Similarly, the predator phage should be able to sustain gastric pH. A farm-worthy and fully potential *Campylobacter* phage must be able to rescue effectively (Connerton et al., 2011). An interesting effort also focuses on the ability of the *Campylobacter* phage to defer clustering in human gut. Twentieth century witnessed a surge in phage therapy wpr to East European part including Russia, but vigorous scientific standards were rather missing (Pelfrene et al., 2016). Phage therapy has been re-emphasized in view of the increasing evolution of antibiotic resistance by the pathogenic bacteria (inclusive of *Campylobacter*) (Stahl et al., 2014). An interesting understanding relates the easy reduction in human *Campylobacter* by a lowered number of *Campylobacter* phages because of comparatively low and transient number of *Campylobacter* occurring during human infection. Additionally, many types of phages (which manifest lytic activity against *Campylobacter*) specific for *Campylobacter* have been isolated and characterized from human activities related sources (majority being the human gut health friendly). Regarding the development of resistance by *Campylobacter* against host specific phages (wpr to *C. jejuni*), their number is a minor component i.e. only 2% acquired resistance against phages according to El-Shibiny at al. (2009). Moreover, a consortium of bacteriophages could be used for maintaining *Campylobacter*-free chicken (a multi-purpose/sources approach i.e. to achieve pan-effective lytic activity against all *Campylobacter* strains. US FDA has been reluctant to give signal for the pre-harvest bacteriophage application as antibacterial entity. Nonetheless, ample relevant work is continued on global basis and these effects may ultimately lead to the acceptance of phage use strategy (Grant et al., 2016; Richard et al., 2019).

Bacteriocins and *Campylobacter*

Another *Campylobacter* clustering incidence reduction option in poultry is the use of generally regarded as safe (GRAS) protein-peptide bioactive secondary metabolites i.e. the bacteriocins. These metabolites may cause reduction in the number of closely related microbes (Rasool and Ajaz, 2017; Quereda et al., 2016). The bacteriocins used against *Campylobacter* are microencapsulated and added to poultry feed. In this connection, four bacteriocins from varied strains of *Paenibacillus polymyxa* and *Bacillus circulans* NRRL B-30644 were described (Svetoch et al., 2005). Messaoudi et al. (2012) exploited bacteriocin extracted from *L. salivarius* SMXD51 in order to reduce *C. jejuni* count in vitro by 2-log10 (in comparison to the control). Purified bacterium OR7 (from *Lactobacillus salivarius* NRRL-B-30644) was given to poultry birds colonized by *C. jejuni* and that lead to reduction of colonization to 6 log10 (Stern et al., 2006). Cole et al. (2006) used bacteriocin B602 (by *P. polymyxa* NRRL B-30509) and OR7 (*L. salivarius* NRRL B-35014) for reducing *C. coli* clustering in turkey. In each trial, the concentration of *C. coli* was found well lowered than the detection levels in the duodenum and cecum. It was suggested that the use of supernatant (instead of purified version) may be better in industrial set ups (because of cost cum labor point of consideration) (Messaoudi et al., 2011). In fact, the direct use of microbial live strains (as probiotics) appears inefficacious for undoing of *Campylobacter* clustering. As regards the development of resistance by *C. jejuni* and *C. coli* against OR-7 and E-760 bacteriocin, the experimental evidences support this development in significance and it was shown that MD (multiple drug) efflux pumps *CmeABC* did facilitate either of the intrinsic and induced resistance to the bacteriocins (Van Hoang et al., 2011). The impact of bacteriocins on the chicken GIT microbiome seems to be of unfounded concern. It is yet to be worked out whether these

bioactive metabolites may contaminate meat produce following harvesting; if yes, the sustainability and effect on human GIT requires investigation (Yadav and Jha, 2019).

CONCLUSIONS

It is well known that drug resistance among *Campylobacter* is on increase and it warrants for searching the non-classical anti-*Campylobacter* treatments. No doubt significant work is underway for developing treatments which could lower down *Campylobacter* clustering in poultry birds or helps do away the acute stage human regulations. Probiotics usage is critical in this connection in addition to *Campylobacter* host specific phages, chicken and human anti-*Campylobacter* compounds, specific vaccines and specific bacteriocins. Many of these have been promising. However, research never becomes static and should continue for a better understanding to approaches against *Campylobacter* in general. Further, mechanisms of Campylobacteriosis (Pathogenesis) and colonization should well be underlined as in the long run it may possibly locate or trace out miscellaneous targets to be exploited for developing the multi prong interventions. We are fully aware regarding the health burden globally inflicted by *Campylobacter* and it is hyper-prone in acquiring antibiotic resistance. So, keep exploring more to be revealed.

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