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Editorial

Vaccines against *Campylobacter jejuni*

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Campylobacter spp. are major foodborne pathogens and a cause of diarrhoea worldwide. It is estimated that approximately 400 million cases of diarrhoea occur worldwide due to *Campylobacter* [1]. *C. jejuni* is the predominant species causing the majority of the infections [2]. *Campylobacter*iosis is endemic in developing countries with a high incidence rate (~40,000-60,000/100,000 population) in children under 5 years of age. The incidence rate of *Campylobacter*iosis is lower in developed countries. In the USA, there are approximately 2.4 million cases of human *Campylobacter* infections every year [3]. *C. jejuni* is a significant cause of travellers' diarrhoea [4].

The clinical manifestations of *Campylobacter* infections are diverse and range from asymptomatic infections to severe diarrhoeas. Individuals living in developing countries usually experience asymptomatic infection or mild diarrhoea, which is mostly watery. On the other hand, individuals living in developed countries, who have not encountered the organism previously, usually experience severe, bloody diarrhoea [5]. *Campylobacter* infections occasionally lead to the development of autoimmune diseases such as reactive arthritis [6] and neurological illness (Guillain-Barre syndrome [GBS] and its variant, Miller Fisher syndrome). There is an increased risk of development of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease following *Campylobacter* diarrhoea [7].

Poultry and domestic animals are the reservoirs of *Campylobacter*. In developed countries, transmission is due to the consumption of improperly cooked poultry meat or drinking contaminated raw milk or water. However, the risk of infection is greater from chickens owing to high levels of consumption of chicken meat [8,9]. In developing countries, close contact with animals and chickens was found to be an important risk factor for acquiring the infection [10,11].

Immunity develops following *Campylobacter* infection. Children < 2 years old in developing countries develop a less severe disease compared to their counterparts in more developed countries [12]. There is also a shift in illness to infection ratio in children 2 to 5 years of age in developing countries with development of colonisation resistance and shortened duration of excretion of the organism during convalescence. Also, children experience a progressive increase in all isotypes of *Campylobacter*-specific serum antibodies in the first two years of life, followed by continued increase in IgA titres, indicative of frequent exposure to the organism and boost in mucosal immunity [13]. In industrialised countries, there is a reduced incidence of *C. jejuni* diarrhoea and increased levels of specific antibody in chronic raw milk drinkers compared to first time drinkers [14]. In human volunteer studies, individuals develop serum and intestinal antibodies to the organism after challenge. Short-term protection from illness upon rechallenge with homologous organism could be correlated with higher levels of serum and intestinal antibodies to the organism [15,16]. Thus, these epidemiological and experimental studies provide evidence of acquired immunity following exposure to *C. jejuni*, lending support for vaccine development. An overall strategy for prevention and control of *Campylobacter* infections involves reduction or prevention of *C. jejuni* contamination at critical entry points along the farm-to-table food chain and providing immunoprophylaxis to the targeted population. One of the ways of reducing food contamination is by reducing the load of the pathogen in its main reservoir, the chickens. Many control measures including vaccination of chickens are being explored [17,18].

C. jejuni strains are extremely diverse. There are two antigenic typing schemes for *C. jejuni*: Lior scheme with 108 serotypes [19] and Penner scheme with >60 serotypes [20]. The antigen in Lior typing scheme is heat-labile whose identity is not known. The antigens in the Penner typing scheme are lipopolysaccharide (LPS) and lipooligosaccharide (LOS) capsule [21]. However, the protective antigens are not clearly defined.

Live attenuated vaccines

The lack of sufficient knowledge about virulence determinants of *C. jejuni* makes the preparation of live attenuated vaccines difficult. Strains that are devoid of LOS with ganglioside mimicry should be chosen carefully to avoid the development of GBS. Moreover, since *C. jejuni* is naturally transformable, *recA* mutant strains have to be used to preclude reversion to wild type. Oral immunisation of mice with an attenuated *Salmonella enterica* serovar Typhimurium vectoring *Campylobacter* PEB1 antigen or CjaA protein failed to protect the animals against intestinal colonisation with the challenge *Campylobacter* strain even though specific serological responses were seen [22,23].

Killed *Campylobacter* whole cell (CWC) vaccines

Mice and rabbits orally immunised with killed CWC organism combined with heat-labile enterotoxin (LT) of *Escherichia coli* as a mucosal adjuvant showed protection against intestinal colonisation by homologous challenge [24,25]. In an oral immunisation and challenge model of mouse infection, CWC-LT formulation was superior to CWC alone in eliciting protection and mucosal immune response [24]. Also, in a monkey model of infection, LT significantly enhanced immune response [26]. In human volunteer studies, a four-dose oral regimen of a killed CWC vaccine combined with a mutant (m) LT – LT(R192G)-with reduced toxicity, induced specific IgA antibody- secreting cells in peripheral blood, faecal IgA antibody and in vitro IFN-γ cytokine production by peripheral blood lymphocytes, deemed important for protection [27]. In a human volunteer study of *C. jejuni* diarrhoea, protection was associated with local antibody

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production in the intestine, and IFN-γ cytokine response by peripheral blood mononuclear cells supporting the notion that Th1 polarisation has a primary role in acquired immunity to *C. jejuni* [28].

Subunit vaccines

A surface protein ACE393 identified by cell surface proteomics approach by ACE BioSciences, Denmark, has entered clinical testing [29]. A recombinant truncated flagellin protein (rFla-MBP) based on the conserved region of flagellin of *Campylobacter coli* VC167 strain used as a vaccine induced antibody response and 31-64% protection against *C. jejuni* in an intranasal mouse model of infection [30] and 60% protection in a ferret model of diarrhoea [27].

CmeC is an essential outer membrane component of CmeABC, a multidrug efflux pump that plays a critical role in antibiotic resistance and in vivo colonisation of *C. jejuni*. Vaccination of chickens with this subunit by subcutaneous or oral route did not confer protection against *C. jejuni* infection [31].

Capsule polysaccharides from two serotypes of *C. jejuni* were conjugated to a carrier protein, CRM, and were subcutaneously administered to mice and New World monkeys. The vaccines elicited robust antibody responses and provided significant homologous protection in mice on intranasal challenge and 100% homologous protection against diarrhoea on orogastric challenge of monkeys [32].

Major outer membrane protein (MOMP)(PorA) is present in an abundant quantity in the organism. It has conserved and variable antigenic epitopes [33]. A recombinant PorA fused to glutathione-S-transferase [GST-PorA] as a vaccine was studied in an adult mouse intestinal colonisation model. The recombinant PorA vaccine when administered with mLT, afforded heterologous protection against three unrelated serotype strains [34]. A nanoparticle encapsulated outer membrane protein when administered subcutaneously, but not orally reduced caecal colonisation of chickens on challenge with *C. jejuni* [35]. A MOMP-based vaccine holds the promise of imparting significant heterologous protection.

Cholera toxin (CT) which is functionally and antigenically related to LT cross-reacts with MOMP of *C. jejuni*, i.e. antibody to CT reacts with MOMPs from different strains of *C. jejuni*, but antibody to MOMP does not react with CT [36]. It has been shown that immunisation with CT afforded significant protection against challenge with *C. jejuni* strains in the adult mouse intestinal colonisation model of infection. The portion of CT responsible for cross-reaction is the B subunit. As the B subunit of CT is a component of the killed oral cholera vaccine, Dukoral, the tantalising possibility remains that Dukoral could be used to protect against *C. jejuni* diarrhoea [37].

As LT is a potent mucosal adjuvant, many experimental vaccines have incorporated it in the vaccine formulations. However, it cannot be used in humans, as it produces diarrhoea. mLT is not a suitable adjuvant as it has residual toxicity [27,38,39]. A double mutant (dm) LT (R192G/L211A) has been shown to retain its adjuvanticity [38,40], but lose its toxicity in a mouse assay [38]. The safety of this double mutant for human use is yet to be established.

Thus different vaccine formulations have been tested in animal models with varying degrees of success. Further testing of promising vaccine formulations in suitable animal models in which *C. jejuni* produces diarrhoea (ferret, monkey) and also in human volunteers is eagerly awaited. Ultimately, vaccines that pass human volunteer study will undergo field trial.

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