Campylobacteriosis: an immunity-focused view

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Abstract

Campylobacteriosis is a debilitating and widespread gastrointestinal disease in both developed and developing countries. In spite of very significant attention to control contamination of food products, relatively little progress has been made in curbing human illness. We propose that differences in human susceptibility, especially via an adaptive immunity response, is a key factor to unravel the continuing, widespread and baffling trends in incidence of campylobacteriosis. This recognizes that Campylobacter species are widespread in the environment (a so-called miasma view) and that although the focus on select contaminated foods has not been definitive, it may provide a means to develop a specific/defined geographic region community-wide immunity approach.

Introduction

Campylobacteriosis is the most common bacterial cause of gastrointestinal disease in humans, with chicken meat regarded as the most common source for human infection (Altekruse et al., 1999; Butzler, 2004; Kotula & Stern, 1984; Nauta et al., 2009; Skirrow, 1991). The disease frequently results in severe diarrhoea, while sequelae may include various forms of paralysis and potentially death e.g. reactive arthritis and Guillain–Barré syndrome (Nichols et al., 2012; Skirrow, 1977). Notably, incidence is primarily sporadic, with relatively few cases associated with outbreaks.

There is a common acceptance that poultry meat products are the most common source of *Campylobacter* infection in humans with one species, *C. jejuni*, typically reported in 80-90% of cases, the balance being primarily *C. coli* with a range of other species being far less common (Altekruse et al., 1999). The current consensus and public health focus is predominantly towards reduction of *Campylobacter*-contamination in chicken products (Umaraw et al., 2017).

This consensus view is supported by some very strong observational and experimental data. However, there remains a plethora of other sources and explanations for campylobacteriosis that make this consensus view problematic (Nelson & Harris, 2017). Faecal contamination by animals and birds is widespread in soil, waterways, irrigated crops, etc as best evidenced by ubiquitous *Escherichia coli* isolation (Edberg et al., 2000). At present, advances in biotyping, especially molecular identification, are providing critical source/patient linkage information. However, this is simply one aspect of the historical competition between germ and miasma theories of disease (Loomis & Wing, 1990). Epidemiological studies need to embrace a wider, broader range of disciplines and views than just risk analysis (Susser, 1998).

The concept of a 'miasma' viewpoint has been suggested to be unhelpful towards reducing the disease burden of campylobacteriosis (Wilson et al., 2006). However, if the single source concept is not producing sufficient results (Nelson & Harris, 2017), perhaps we should consider a broader scope of investigation.

We reconsider campylobacteriosis epidemiology and attempt a rational alternative view to the current risk analysis focus. Specifically that campylobacteriosis sporadic incidence patterns arise primarily as a result of differences in individual immune susceptibility plus microbe exposure.

Immune Susceptibility

Relatively large proportions of any population exhibit or develop comparative immunodeficiencies and are therefore more vulnerable to diseases (Lund & O'Brien, 2011). These are commonly the very young, elderly or otherwise immune-compromised individuals. Use of antibiotics appears also to increase susceptibility to infection, especially when used in the period 1 month to 2 years prior to infection (Koningstein et al., 2011; Neal et al., 1996).

Proton pump inhibitors have long been recognised to increase risk for campylobacteriosis (Bouwknegt et al., 2014; Neal et al., 1996; Tam et al., 2009; Wei et al., 2017). The slight increase in campylobacteriosis rates in the elderly is commonly thought to be associated with a natural age associated reduced stomach acidity, but evidence indicates this seldom occurs (Hurwitz et al., 1997). Therefore other risk factors in this age group also need to be investigated. Differences in dietary fibre intake appears to affect the ability of *Campylobacter* to invade gut epithelium cells (Masanta et al., 2013), possibly through changing the concentration of short chain fatty acids (SCFA) derived from the gut microbiota.

Campylobacter outbreak cases are much less common and typically involve a larger group of cases clustered via a common point source. This may be from specific food stuffs, such as liver (Edwards et al., 2014), commercial catering (Mazick et al., 2006; Osimani & Clementi, 2016), dairy products (Taylor et al., 2013) and contaminated water sources (Gallay et al., 2006; Kuusi et al., 2004). Therefore outbreaks probably represent increased opportunity for infection by providing an infectious dose

sufficiently large to overwhelm innate and/or adaptive protective mechanisms of most people.

Susceptibility to infection in a campylobacteriosis context can therefore relate to one or more specific changes. These include:

- reduced immune response to infection induced by disease, pathogen or medication associated immunodeficiencies
- prior use of antibiotics
- changes in natural barriers to infection such as proton pump inhibitor medication
- opportunity for infection as clearly evidenced in outbreak case clusters, i.e. overwhelming infectious dose or novel strains.

Immunity

An innate immune reaction to *Campylobacter* infections has been suggested previously. For example "individual susceptibility" (Rodrigues et al., 2000), "previous exposure may confer protection against subsequent infection" (Forbes et al., 2009), and "population immunity" (Nichols et al., 2012). Development of such immune reactions is already exploited in animal health (Sahin et al., 2017) against *Campylobacter* in ovine (Fenwick et al., 2000) and bovine (Hoffer, 1981) farming using commercially available vaccines, suggesting an opportunity for human protection too (Scott, 1997; Tribble et al., 2010). An equivalent vaccination for chickens, while receiving considerable investment, has failed to prove as effective (De Zoete et al., 2007; Meunier et al., 2016).

Specific immune responses in humans to *Campylobacter* infection have been reported (Baqar et al., 2001; Cawthraw et al., 2002). Surveys indicate an apparent immunity associated with prior and continued exposure, for example through occupational exposure (Cawthraw et al., 2000; De Perio et al., 2013; Ellström et al., 2014; Vegosen et al., 2015; Wilson, 2004), including dose-response development of immunity markers. Sero-epidemiological surveys indicate very high exposure to *Campylobacter* infection by early adulthood within European populations (Ang et al., 2007; Ang et al., 2011; Teunis et al., 2013). However, any immunity from prior exposure appears to be strain specific (Kirkpatrick et al., 2013), is dose related and degrades fairly rapidly (Tribble et al., 2010).

Within developing countries, immunity markers are prevalent in older populations without associated diarrhoea symptoms (Coker et al., 2002; Havelaar et al., 2009). This effect is presumably associated with continued exposure and maintenance boosting of immunity, similar to that reported through occupational exposure in developed countries.

Discussion

Humans are exposed to a very wide range of species and biotypes of *Campylobacter*, from very broadly defined sources and via mechanisms clearly far wider than food contamination (Nelson & Harris, 2017). Within this exposure pattern, individuals also vary in susceptibility. A broader discussion beyond simply controlling *Campylobacter* contamination in specific food sources is required in order to tackle combating campylobacteriosis.

Recognition of the presence of an immune response reaction in humans indicates the potential for some sort of prophylactic immune-system priming. Development of killed whole-cell vaccine for oral treatment has shown promise in animal models (Baqar et al., 1995), but vaccines for human use remain problematic (Jagusztyn-Krynicka et al., 2009). Whole-cell killed vaccines have shown particular promise against other diseases, especially where there is endemicity and an environmental exposure, such as those against *Cholera* (Kirpich et al., 2017) or *Helicobacter pylori* (both vibrios and so close relatives of *Campylobacter*) (Summerton et al., 2010).

In some respects, properly cooked (*Campylobacter*) contaminated foodstuffs could in fact prove to have the same whole-cell killed vaccine effect (Tam et al., 2009), thus explaining the source of frequent exposure without illness as evidenced by sero-epidemiology studies (Teunis et al., 2013). Thus, in a counter intuitive manner, the current efforts to eradicate *Campylobacter* from chicken products may in fact prove counterproductive in some respects by reducing the frequency of our ongoing exposure and immune priming to the bacteria. This prior immune priming may provide some protection against larger infectious dose cases, including outbreaks, but still largely does not explain the much larger proportion of sporadic cases.

The benefit of killed whole-cell vaccines is that a broad range of biotypes, typical of the specific region targeted for protection, can probably be developed relatively quickly and cheaply. Medication via a common food, such as a milk drink or freeze-dried formulation for oral dosage, might prove one means of establishing population-level immunity. In particular, increased risk immuno-compromised groups might obtain particular benefit from such protective treatment. The relatively high incidence of campylobacteriosis in travellers could similarly be addressed by oral dosage of locally prepared 'medicated' food or drink when travelling. Eating properly cooked local produce could also be expected to provide more immunity to more commonly encountered local environmental strains. Interestingly, this approach would support the 'Slow Food' movement which encourages farming of plants, seeds, and livestock characteristic of the local ecosystem.

The two most common environmental species of *Campylobacter*, *C. jejuni* and *C. coli* (Jones et al., 2017) are the most likely to infect local chicken production facilities. This presumably then means regular consumption of properly cooked chicken foods derived from infected chickens has quite possibly been acting as a natural killed whole-cell vaccine for the human population also exposed to the same environmental *Campylobacter* strains. Broad strain variation load and early colonisation is common in free-range flocks, unlike common single strain colonisation in high density flocks (Cawthraw & Newell, 2010).

However, modern increased biosecurity practices in mass poultry meat production is both removing this vaccine option through aiming for *Campylobacter*-free meat production, and severely curtailing the range of local environmental strains encountered. This raises interesting ethical dilemmas, if this common food product has such a community-wide immune stimulating protective potential, then deliberately introducing practices, such as free-range farming, in order that a wide range of local environmental strains of *Campylobacter* are present at slaughter makes sense. However, this could also increase the risks of point source outbreak and other cross-contamination events occurring.

Conclusion

While it is sometimes difficult to establish a specific source, outbreaks of campylobacteriosis are generally clear cut and essentially resolve to specific point sources. The far higher incidence of sporadic cases is more problematic to explain, especially considering the difficulties with security of source attribution via poultry meat contamination, although there is little doubt this is very likely to be a contributing source. However, the emphasis on attempting to control poultry as the primary source has so far contributed relatively little to reducing the incidence of camplyobacteriosis in the long term.

Advances in understanding of immune responses, not only for the development of vaccines in animals, but also understanding the otherwise baffling sporadic incidence pattern in humans, may contribute far more. In this regard, recognising the broad environmental prevalence of *Campylobacter* species via a 'miasma' view, and applying an immunological lens, may move the debate forward. It could return the focus to reducing the incidence of campylobacteriosis, by understanding the environmental ubiquity of the bacteria and associated ongoing priming of our immune system rather than attempting to eliminate this organism from food sources that has so far been only modestly effective.

Failure to embrace this concept is more likely to entrench the current chicken source only belief concept approach which 'is a riddle, wrapped in a mystery, inside an enigma' (Churchill, 1939); but perhaps there is a key, in this framework of a 'miasma'-induced immunity.

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