SHORT REPORT
Sexual dimorphism in campylobacteriosis

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SUMMARY

Sexual dimorphism in infectious diseases whereby disease incidence is more prevalent in one gender has been reported repeatedly in the scientific literature. Both behavioural and physiological differences have been suggested as a cause of this gender bias but there is a paucity of data to support either of these viewpoints. Here it is hypothesized that for campylobacteriosis physiological factors play an important role in the higher incidence in males. We demonstrate in the human population (from several countries in three continents) that this bias exists in young children (<1 year) where behavioural differences between genders are likely to be minimal. Further we demonstrate this difference in an animal model where both infection rates and shedding rates of the organism are greater in male mice.

Human campylobacteriosis is a leading cause of bacterial gastroenteritis worldwide infecting an estimated 2.45 million people annually in the United States alone [1]. *Campylobacter* is ubiquitous in the environment and is commonly carried and shed by farm animals, wild birds and household pets [2]. Risk factors for human infection include eating undercooked meat (particularly chicken), travelling abroad and visiting or living on a farm [3].

A number of studies have demonstrated that reported disease is more common amongst males, e.g. in the United States [4] and Sweden [5]. A number of putative reasons to explain this sexual dimorphism have been postulated and these include male ineptness in food preparation and consumption [6], differences in the likelihood of seeking medical care [3] as well as physiological differences [3]. Further, higher incidence of Guillain–Barré syndrome (a neural disorder causing acute neuromuscular paralysis) in males aged >55 years with a history of campylobacteriosis, has also been reported [7]. However, it is widely acknowledged that the reasons for the gender differences in *Campylobacter* infections are unclear [8]. Here we collate disease reports from different regions across the world to show the consistent gender differences exhibited in human campylobacteriosis and in particular in young children. We then use a mouse model under controlled laboratory settings to minimize the effects of behaviour and environment to address the question whether physiological factors influence sexual dimorphism in this disease.

Annual reports (1997–2004) of human campylobacteriosis stratified by both age and gender were
obtained from the Grampian region of Scotland (Aberdeen Royal Infirmary), New Zealand [Institute of Environmental Science and Research Ltd (ESR)], Norway (Nasjonalt folkehelseinstitutt) and Canada Public Health Agency. These data were entered into Excel where standard errors were calculated and t tests were performed to determine the significance of gender differences.

Figure 1 shows that the male incidence is significantly greater when considering the whole population of each country/region studied (paired, one-sided t test, $P < 0.001$). Similarly, for children aged <1 year the male incidence was found to be significantly greater than for females (paired, one-sided t test, $P < 0.05$).

Since wild-type mice are refractory to infection, we used a recently established animal model of infection that makes use of mice defective in the Myd88 adaptor protein [9]. These animals are efficiently and persistently colonized by Campylobacter jejuni. Age-matched Myd88 $-/-$ male and female mice were orally infected with $10^9$ C. jejuni, and colonization was evaluated by measuring bacterial shedding in faecal samples (Fig. 2).

One week post-inoculation 100% (5/5) male mice were heavily colonized by C. jejuni whereas only 25% (1/4) female mice shed the target microorganism. In addition, the number of bacteria recovered in faecal samples was significantly ($P < 0.0001$, Mann–Whitney test, two-tailed) higher in males than in females. The increased colonization of male mice continued over time and at week 4 the levels of colonization of males was $\sim 4000$-fold higher than females. Four weeks after infection, mice were sacrificed and the number of colony-forming units (c.f.u.) in different tissues was quantified. Higher numbers of c.f.u. were recovered in the tissues of all the male mice. In contrast relatively modest numbers of c.f.u. were recovered from only one of the four female mice. These data indicate that male Myd88 $-/-$ mice are more susceptible to infection and colonization by C. jejuni than female mice.

**Fig. 1.** Sexual dimorphism of human campylobacteriosis averaged over the period 1997–2004 (error bars are standard errors of the mean, $n = 8$ years) for (a) Canada (94 280 cases), (b) Grampian region of Scotland (5986 cases), (c) New Zealand (86 670 cases) and (d) Norway (18 202 cases).
The increased level of colonization and incidence in male mice, where the effects of both behavioural and environmental factors have been minimized, underpin the hypothesis that physiological factors play a key role in sexual dimorphism in mice. Testing this hypothesis using a mouse model for \textit{C. jejuni} infection, also allowed us to examine the effect of gender factors under controlled laboratory conditions and uniform genetic background. Further, the fact that these gender differences also occur in young children (aged $<1$ year), where at this age behavioural differences are likely to be minimal, also demonstrates that physiological differences are important in humans.

Higher rates of colonization in male mice have also been found for the related pathogen \textit{Helicobacter pylori} and it has been suggested that this sexual dimorphism may contribute to the higher rates of gastric cancer seen in male patients [10]. The influence of gender in colonization dynamics of the related pathogen \textit{Helicobacter hepaticus} has also been reported [11]. Moreover, higher incidence rates in human males ($<1$ year old) has been observed for a number of other infectious diseases including shigellosis, salmonellosis, viral meningitis and viral hepatitis and this has been attributed to an increased deficiency in immunological competence in the male population [12].

Sexual dimorphism changes with age in humans, with male incidence peaking in the 10–14 years age group. The reason why it peaks at this age is unknown. It is possible that this may be behavioural but physiological reasons associated with male maturation are also possible. The male:female incidence ratio is lowest in the 20–29 years age group and this phenomenon has also been observed for shigellosis and salmonellosis [12] and it has been suggested that this is due to higher exposure in females of childbearing age to faeces from infected small children. The results presented here suggest that this could also be the case for \textit{Campylobacter} but further epidemiological investigations are required to investigate the range of behavioural and physiological factors that may affect these results.

It has been reported [13] that human \textit{Campylobacter} cases that present with vomiting and/or bloody diarrhoea are more likely to need hospitalization and are more likely to be female. Green [12] postulates that male predominance is strongest in diseases where there are large numbers of asymptomatic cases and that this reduces for diseases which are mainly symptomatic. We describe here a male predominance for \textit{Campylobacter} infections where the number of asymptomatic, or certainly very mild cases not being reported, are large (e.g. it has been reported that for every one case of \textit{Campylobacter} in England and Wales another seven are unreported [14]). However, it appears that when only those cases with more immediate severe symptoms are considered, then females may be at greater risk. The reasons for this are unknown but are likely to be physiological.

Our animal model, which minimizes differences in behaviour and environment between the sexes, demonstrates sexual dimorphism of infection in mice when exposed to \textit{C. jejuni}. This can be attributed to differences in physiological response between the sexes. For example, it has been reported that accelerated intestinal epithelial cell turnover can increase \textit{Trichuris} parasite expulsion and that this mechanism is more effective in females than males.
[15]. It is not known whether a similar mechanism contributes to the gender differences in susceptibility to C. jejuni infection here. However, what we have established in this paper is the likelihood that a physiological mechanism does exist. Human epidemiological data, which demonstrate higher rates of Campylobacter infection in males across most age groups, but in particular for young children where the influence of behaviour is likely to be smallest, is parsimonious with the view that variation in human physiological response between the sexes is a major reason for the gender difference in this age group. Epidemiological investigations involving, for example, case-control studies and also testing of drugs should use sex-matched populations to minimize confounding. Further, this gender difference should be considered when studying the pathogenicity of this organism and when investigating the incidence of the disease in human populations.

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DECLARATION OF INTEREST

None.

REFERENCES