Sex differences in campylobacteriosis incidence rates at different ages - a seven country, multi-year, meta-analysis. A potential mechanism for the infection.

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Manfred S Green manfred.s.green@gmail.com
University of Haifa
Corresponding Author
ORCiD: 0000-0002-9753-5612

Naama Schwartz
University of Haifa School of Public Health

Victoria Peer
University of Haifa School of Public Health

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Abstract

Background There is evidence that females mount a more efficient immune response to gram-negative bacteria. The objectives of this study were to determine whether there are consistent sex differences in the incidence rates of campylobacteriosis at different ages in different countries.

Methods We obtained data on incidence rates of campylobacteriosis by sex and age group over a period of 11-26 years from seven countries. Male to female incidence rate ratios (IRR) were computed by age group, country and time period. For each age group, we used meta-analytic methods to combine the IRRs. Sensitivity analysis was used to test whether the results are stable and robust. Meta-regression was conducted to the estimate the effects of age, country, and time period on the IRR.

Results In the age groups <1, 1-4, 5-9, 10-14, 15-44, 45-64 and 65+ years old, the pooled IRRs (with 95% CI) were 1.31 (1.26-1.37), 1.34 (1.31-1.37), 1.35 (1.32-1.38), and 1.73 (1.68-1.79), 1.10 (1.08-1.12), 1.19(1.17-1.21), 1.27 (1.24-1.30), respectively. For each age group, the excess campylobacteriosis incidence rates in males is remarkably consistent for countries and time-periods, and in meta-regression analysis, age group was responsible for almost all the variation in the IRRs.

Conclusions The male predominance in campylobacteriosis incidence rates starts in infancy. This suggests that this is due, at least in part, to physiological or genetic differences and not just behavioural factors. These findings can provide clues to the mechanisms of the infection, and could lead to more targeted treatments and vaccine development.
Introduction

Campylobacteriosis, caused by the non-spore-forming, gram-negative rod, Campylobacter jejuni, is one of the most common causes of bacterial gastroenteritis (1). The disease can be debilitating, with occasional severe complications such as toxic mega-colon, sepsis and the Guillane-Barre syndrome (1). Based on serosurveys, the subclinical incidence of campylobacteriosis is much higher than the incidence of clinically overt disease (2). Transmission is mainly food-borne, particularly from uncooked poultry products (3). Fecal-oral transmission among humans can occur such as through person-to-person sexual contact (4) and contamination by food handlers and it is a common cause of travellers’ diarrhea (3,5).

The mechanism of campylobacteriosis infection is complex and the variability of disease outcomes is thought to be linked to the immune response induced by the bacteria (6).

The virulence factors induce a pro-inflammatory response that is initiated by the intestinal epithelial cells, propagated by innate immune cells and modulated by the cells of the adaptive immune response (6). Mortality rates from sepsis appear to be lower in females (7). Recently, Zeng et al (8) demonstrated a more efficient immune response to gram-negative bacteria in female mice.

There are isolated reports suggesting higher campylobacteriosis incidence rates in males, based largely on hospital-based studies in individual countries and for selected age groups (9, 10). However, possible sex differences in the incidence of the disease have not been rigorously evaluated in large, representative databases with reliable denominators. This information could improve our understanding of the
mechanism of the host response to the infection. In the present study, we analysed the magnitude and consistency of the sex differences in the incidence of campylobacteriosis in different age groups, for a number of countries and time periods, using national data.

Methods

Source of data

We restricted the selection of countries included in the study to those for which campylobacteriosis is a notifiable disease, have reliable reporting systems, have advanced health systems with adequate facilities for diagnosis of the disease and provide data by age and sex for a number of years. These restrictions should ensure that the database is of good quality. Data on reported cases of campylobacteriosis by age, sex and calendar year were obtained from relevant government institutions for seven countries. Data for Australia were obtained from the National Notifiable Diseases Surveillance System (NNDSS) (11), for Canada from Public Health Agency of Canada (PHAC) (12), for Finland from the National Institute for Health and Welfare (THL) (13), for Germany from the German Federal Health Monitoring System (14), for Israel from the Ministry of Health, for New Zealand, from the Institute of Environmental Science and Research (ESR) (15), and for Spain from the Spanish Epidemiological Surveillance Network (16). Information about the population size by age, sex and year was obtained for Australia from ABS.Stat (17), for Canada from Statistics, Canada database (18), for Finland from the Statistics Finland's PX-Web databases (19), for Germany from the German Federal Health Monitoring System (20), for Israel from Central Bureau of Statistics (21), for New Zealand from Statistics New Zealand (22), and for Spain from the Demographic Statistics
Database (23).

Ethics

National, open access aggregative and anonymous data were used and there was no need for ethics committee approval.

Statistical analyses

Campylobacter incidence rates (IR) per 100,000 were calculated by sex, age group, for each country and calendar year using the number of reported cases divided by the respective population size and multiplied by 100,000. The age groups considered were <1 (infants), 1-4 (early childhood), 5-9 (late childhood), 10-14 (puberty), 15-44 (young adulthood), 45-64 (middle adulthood) and 65+ (senior adulthood) years old. The surveillance systems in Canada and New Zealand used similar age-groups except for the following: 15-39, 40-59 and 60+. For Australia and Finland data are missing for ages 0-1 and 1-4. The male to female incidence rate ratio (RR) was calculated by dividing the incidence rate in males by that of females, by age group, country and time period.

We used meta-analysis methodology to evaluate the overall magnitude of the sex differences in the incidence of campylobacteriosis by age group, across different countries and over a number of years. The outcome variable was the male to female incidence RR (IRR). The data presented (forest plots) are the IRRs by age group, for two years intervals for each country. The reported period for all countries was between 1991 and 2016, and was divided into two year intervals (aside from data for each individual year). For each age group, the IRRs for each country were pooled over time periods and then the pooled RRs for each country were combined.

Heterogeneity was evaluated using Cochran's Q statistic, Tau^2 and I^2 was used to estimate the between-study variance. If the Q test yielded a p < 0.1, and/or
I² ≥ 50%, The random effects model (DerSimonian and Laird) was used to estimate pooled IRRs and 95% confidence intervals (CI), otherwise the fixed model was used.

To evaluate the effect of individual county and reported years on the risk of campylobacteriosis, we performed leave-one-out sensitivity analysis and recomputed the pooled IRRs. We performed the Egger test for asymmetry for testing for a possible imbalance in the studies around the pooled IRR.

In order to explore associations of the incidence IRRs with age-group, country and time period, meta-regression analyses were performed. The meta-analyses and meta-regressions were carried out using STATA software version 12.1 (Stata Corp., College Station, TX).

Results

Descriptive statistics

The summary of male and female incidence rates (per 100,000 populations) in different countries for each age group is presented in Table 1.

Insert Table 1

In every country, in all age groups the incidence rates of Campylobacter were higher in males compared to females.

Meta-analyses by age group

The forest plot for infants is shown in Figure 1.

Insert Figure 1
Overall there was a 31% excess incidence rates in males and the pooled IRRs varied from 1.21 in Germany to 1.52 in Israel. The forest plot for age 1-4 is shown in Figure 2.

**Insert Figure 2**

There was an overall excess of 34% incidence rates in males, and varied between 22% in Germany and 51% in Israel. The forest plot for age 5-9 is shown in Figure 3.

**Insert Figure 3**

There was an overall excess incidence rate of 35% in males, varying between 21% in Germany and 47% in Israel. The forest plot for puberty (10-14) is shown in Figure 4.

**Insert Figure 4**

There was an overall 73% excess incidence rates in males, varying from 47% in Finland to more than double in males in Israel. Due to space considerations, the forest plots for the older age groups are presented in the appendix. For young adults (15 to 44 years) males had a 10% excess in incidence rates (see additional file 1). The pooled IRRs varied from no excess in Germany to 19% in Spain. For middle-age adults (45-64 years), males had a 19% excess in incidence rates (see additional file 2). The pooled IRRs varied from a 5% excess in Israel to a 51% excess
in Spain. For age 65+ years, males had a 27% excess in incidence rates and ranged from 13% in Israel to 72% in Spain. (see additional file 3).

**Sensitivity analysis**

To evaluate the effect of individual countries and years on the pooled IRR, we performed leave-one-out sensitivity analysis and recomputed the pooled IRRs. After omitting one country at a time, the pooled IRR’s remained very similar (Table 2).

**Insert Table 2**

Similar results were obtained after omission of another group of years at a time (See Appendix B, Figure B1) Thus, no single country or particular groups of years substantially influenced the pooled IRRs. This confirms that the results of this study are stable and robust.

**Meta-regression analysis**

Meta-regression results revealed that the age groups (p<0.0001) contributed to almost all the source of heterogeneity, with very little contributed by countries or years. There was no significant difference in the pooled IRR between infancy to early/late childhood, and senior adulthood (p>0.05).

**Asymmetry analysis**

Egger's test was used to check the existence of asymmetry in the contribution of countries and years in the analyses. The test was not significant for infants (p=0.427), in middle adulthood (p=0.234), and in senior adulthood (p=0.746). Evidence of asymmetry was observed for the early and late childhood, puberty and young adulthood with p < .0001 (See additional file 4).
Discussion

Based on meta-analyses of national data from seven countries, over a period of 11–26 years, we found that the incidence rates for campylobacteriosis were 31%, 34%, 35% and 73% higher in males in infancy, young and late childhood and puberty, respectively. In young, older and senior age adults, they were 10%, 19% and 27% higher in males. The findings are remarkably consistent over countries and over a number of years. Our findings considerably extend those from isolated studies conducted largely on hospital-based data at specific periods in different countries (9, 10).

A major strength of the study is that it is based on national data with very large populations and consequently large numbers of cases and incidence rates based on reliable denominators. Selection bias has been minimized by using national data over different time periods, which should be representative of each country. The inclusion of seven countries, each evaluated over a number of years, allowed us to evaluate the consistency of the findings over different populations and many years. We do not believe that that excluding countries that have poor diagnostic facilities or reporting has created an important source of selection bias which would affect the sex differences in incidence rates. Since the clinical manifestations of campylobacteriosis vary widely, there could be significant under-reporting. However there is no reason to suspect that the reporting is related to the sex of the patient. Finally, differences that may exist in the laboratory methods used to confirm infection should also be unrelated to the sex of the patient.

While this study cannot address the mechanisms underlying the sex differences in the incidence of campylobacteriosis, it is possible to speculate about possible
cultural, behavioural, genetic and hormonal factors. A male predominance has been reported in the incidence of certain other infectious diseases, mainly in children (24,25). Regarding possible cultural factors, in the countries in this study, there is no evidence that the sex of the child influences the medical care given for acute infections. Similarly, there is no evidence to suggest that in these countries, adult men are more likely than women to seek medical care for acute conditions of comparable severity. If anything, studies have shown that women are more likely to seek medical care (26). Sex differences in exposure due to behavioural factors are unlikely to play a part in infants and very young children. In adults, exposure resulting from the care of young children could vary by sex, but this is more likely to bias the results towards females. In any event, the transmission of Campylobacter is mainly through food and water, and person-to-person spread is considered to be uncommon (1,3,5). In the older age groups, it is conceivable that males may be more likely to be exposed as a result of consumption of inadequately cooked food eaten outside of the home (27).

Regarding genetic factors, females generally exhibit elevated humoral and cell-mediated immune responses compared to males, and this may be related to X-linked chromosome expression. X chromosomes contain genes associated with immune system and presence of two X chromosomes plays a major role in enhancing both innate and adaptive immune responses (28).

Genetic factors could play a part through an interaction with sex hormones. Estradiol promotes innate immune signaling pathways, including macrophages, dendritic cells (DCs), granulocytes, and lymphocytes cell development. The hormone also enhances production of pro-inflammatory cytokines and chemokines in response to TLR ligand stimulation of dendritic cells and macrophages, a
phenomenon that may explain the superior immune response to infection in females (29–31). Testosterone has the effect of depressing the innate and adaptive immune response (32). Thus it is conceivable that sex hormones are implicated in the mechanism of infection by Campylobacter jejuni. C. jejuni interferes with host innate immune signaling and the flagellins, FlaA and FlaB have been found to activate the innate immune receptor Toll-like receptor 5 (TLR5) (33). Al-Banna et al (6) have proposed that the immune response induced by C. jejuni induces a cascade of pro-inflammatory cytokines initiated by intestinal epithelial cells and innate cells, promoted by antigen-presenting cells and enhanced by T cells, but resolved by anti-inflammatory cytokines. Estrogen is known to impact on the cytokines in the immune response of innate immunity and anti-inflammatory cytokines (34). They could thus modify the response to infection and contribute to the sex differences in the incidence rates from campylobacteriosis.

Zeng et al (8) recently demonstrated that innate antibodies against enteropathogenic Escherichia coli (EPEC) were present only in female mice after puberty and developed as a response to estrogen. They showed that these antibodies enabled Kupffer cells to capture circulating EPEC and were not dependent on previous exposure to the antigen. Thus, differences in sex hormone levels could play a significant biological role in the immune response to infection with C. jejuni and result in higher incidence rates of campylobacteriosis in males. Prior to puberty, it is not clear to what extent sex hormones play a role in the sex differences in disease. In the first year of life, sex hormone levels differ between males and females during the so-called “mini-puberty”. It is characterized by higher testosterone levels in boys at 1-3 months of age which decline at 6-9 months of age, whereas in girls, oestradiol levels remain elevated longer (35). Thus, sex
hormones could conceivably play a role in affecting immune cells even in the first year of life and may be "carried over" from infancy into early childhood.

As mentioned earlier, a serious complication of campylobacteriosis is the Guillain-Barré syndrome. It is interesting to note that there are reports that the Guillain Barre syndrome is also more common in males (36). It is not clear whether the excess incidence of Guillain-Barré syndrome in males is confined solely to those cases occurring as result of campylobacteriosis.

In conclusion, the remarkably consistent excess incidence of campylobacteriosis in males, particularly in infants and very young children, suggests and that sex-specific factors influence the manifestation of clinical disease. These findings should stimulate research on sex as a biological variable in the pathogenesis of campylobacteriosis.

References

1. Kaakoush NO, Castaño-Rodríguez N, Mitchell HM, Man SM. Global Epidemiology of Campylobacter Infection. Clin Microbiol Rev 2015;28:687-720

2. Ang CW, Teunis PF, Herbrink P, et al. Seroepidemiological studies indicate frequent and repeated exposure to Campylobacter spp. during childhood. Epidemiol Infect 2011;139:1361-8

3. Bolton DJ. Campylobacter virulence and survival factors. Food Microbiol 2015;48:99-108

4. Mook P, Gardiner D, Kanagarajah S, et al. Use of gender distribution in routine surveillance data to detect potential transmission of gastrointestinal infections among men who have sex with men in England. Epidemiol Infect 2018;146:1468-77
5. Kuhn KG, Nielsen EM, Mølbak K, Ethelberg S. Determinants of sporadic Campylobacter infections in Denmark: a nationwide case-control study among children and young adults. Clin Epidemiol 2018;10: 1695-1707

6. Al-Banna NA, Cyprian F, Albert MJ. Cytokine responses in campylobacteriosis: Linking pathogenesis to immunity. Cytokine Growth Factor Rev 2018; 41:75-87

7. Kahlke V, Dohm C, Mees T, Brötzmann K, Schreiber S, Schröder J. Early interleukin-10 treatment improves survival and enhances immune function only in males after hemorrhage and subsequent sepsis. Shock 2002; 18: 24-8

8. Zeng Z, Surewaard BGJ, Wong CHY, et al. Sex-hormone-driven innate antibodies protect females and infants against EPEC infection. Nat Immunol 2018;19:1100-11

9. Strachan NJ, Watson RO, Novik V, Hofreuter D, Ogden ID, Galán JE. Sexual dimorphism in campylobacteriosis. Epidemiol Infect 2008; 136:1492-5

10. Weinberger M, Moran-Gilad J, Rokney A, et al. Molecular epidemiology of Campylobacter jejuni infection in Israel - a nationwide study. Clin Microbiol Infect 2016; 22:1005.e9-1005.e15

11. National Notifiable Diseases Surveillance System (NNDSS), Department of Health: http://www9.health.gov.au/cda/source/rpt_5_sel.cfm. Accessed on April 1, 2018.

12. Public Health Agency of Canada: https://www.canada.ca/en/public-health.html. Accessed on June 1, 2018.

13. National institute for health and welfare (THL):https://thl.fi/ttr/gen/rpt/tilastot.html. Accessed on May 1, 2018.

14. German Federal Health Monitoring System: http://www.gbe-bund.de/gbe10/pkg_isgbe5.prc_isgbe?p_uid=gast&p_aid=0&p_sprache=D.
15. Environmental Science and Research (ESR) for the Ministry of Health:
https://surv.esr.cri.nz/surveillance/annual_surveillance.php. Accessed on March 30, 2018.

16. Instituto de Salud Carlos III: http://www.eng.isciii.es/ISCIII/es/contenidos/fd-servicios-cientifico-tecnicos/fd-vigilancias-alertas/fd-enfermedades/enfermedades-declaracion-obligatoria-informes-anuales.shtml. Accessed on March 1, 2018.

17. Stat (Australian Bureau of Statistics): http://stat.data.abs.gov.au/Index.aspx?DatasetCode=ABS_ERP_ASGS2016. Accessed on May 15, 2018.

18. Statistics, Canada, CANSIM database:
https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1710010201. Accessed on June 1, 2018.

19. Statistics Finland's PX-Web databases:
http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__vrm__vaerak/statfin_vaerak_pxt_0
rxid=2f968705-bdaa-48b1-9d5a-d4985ead7d40. Accessed on April 15, 2018.

20. German Federal Health Monitoring System: http://www.gbe-bund.de/oowa921-install/servlet/oowa/aw92/WSO100/_XWD_FORMPROC?
TARGET=&PAGE=_XWD_106&OPINDEX=20&HANDLER=_XWD_CUBE.SETPGS&DATACUBE=
Accessed on February 1, 2018.

21. Central Bureau of Statistics:
http://www.cbs.gov.il/reader/shnatonhnew_site.htm?
sss=%E4%EE%F9%EA&shnaton_scan=45. Accessed on March 1, 2018.

22. Stats NZ, Infoshare:
http://archive.stats.govt.nz/infoshare/SelectVariables.aspx?pxID=b854d8a2-
23. Demographic Statistics Database (United Nations Statistics: Division):
http://data.un.org/Data.aspx?d=POP&f=tableCode%3A22. Accessed on April 1, 2018.

24. Green MS. The male predominance in the incidence of infectious diseases in children: a postulated explanation for disparities in the literature. Int J Epidemiol 1992; 21: 381-86

25. Peer V, Schwartz N, Green MS. Consistent, excess viral meningitis incidence rates in young males: a multi-country, multi-year, meta-analysis of national data. The importance of sex as a biological variable. EClinicalMedicine 2019 (in press).

26. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. J Fam Pract 2000;49: 147-52

27. Kearney JM, Hulshof KF, Gibney MJ. Eating patterns - temporal distribution, converging and diverging foods, meals eaten inside and outside of the home - implications for developing FBDG. Public Health Nutr 2001;4: 693-98

28. Pinheiro I, Dejager L, Libert C. X-chromosome-located microRNAs in immunity: Might they explain male/female differences? The X chromosome-genomic context may affect X-located miRNAs and downstream signaling, thereby contributing to the enhanced immune response of females. BioEssays 2011; 33:791-802

29. Seillet C, Rouquie N, Foulon E, et al. Estradiol promotes functional responses in inflammatory and steady-state dendritic cells through differential requirement for activation function-1 of estrogen receptor alpha. J Immunol 2013; 190: 5459-70
30. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol 2008;8:737-44

31. Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev 2000; 24: 627-38

32. Trigunaite A, Dimo J, Jørgensen TN. Suppressive effects of androgens on the immune system. Cell Immunol 2015; 294:87-94

33. Faber E, Gripp E, Maurischat S, et al. Novel immunomodulatory flagellin-like protein FlaC in Campylobacter jejuni and other Campylobacterales. mSphere 2015; 1. pii: e00028-15

34. Schneider AH, Kanashiro A, Dutra SGV, et al. Estradiol replacement therapy regulates innate immune response in ovariectomized arthritic mice. Int Immunopharmacol 2019;72:504-10

35. Kuiri-Hänninen T, Sankilampi U, Dunkel L. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. Horm Res Paediatr 2014; 82:73-80

36. Delannoy A, Rudant J, Chaignot C, Bolgert F, Mikaeloff Y, Weill A. Guillain-Barré syndrome in France: a nationwide epidemiological analysis based on hospital discharge data (2008-2013). J Peripher Nerv Syst 2017; 22:51-58

Tables

Table 1: Details of the countries included in the meta-analysis, by sex and age group - total cases, population size and incidence rates (IR) per 100 000

| Age group | Country     | Years    | n/N        | IR   | Males | Females |
|-----------|-------------|----------|------------|------|-------|---------|
| <1        | Canada      | 1994-2015| 2045/4066314| 50.3 | 1539/ |
| Country     | Period         | Data Points | Average (in 1000s) | Average (in 1000s) |
|-------------|----------------|-------------|--------------------|--------------------|
| Germany     | 2001-2016      | 4786/4847   | 376.8              | 1576/1             |
| Israel      | 1991-2016      | 6669/177000 | 376.8              | 9811/6             |
| New Zealand | 1997-2015      | 2128/576900 | 368.9              | 7520/5             |
| Spain       | 2005-2015      | 7054/2679186| 263.3              | 12341/1            |
| 1-4         |                |             |                    |                    |
| Canada      | 1994-2015      | 11480/16718349 | 68.7            | 8252/1             |
| Germany     | 2001-2016      | 30709/23509315 | 130.6            | 23847/5            |
| Israel      | 1991-2016      | 15607/6843500 | 228.1              | 9811/1             |
| New Zealand | 1997-2015      | 10525/2308880 | 455.9              | 7520/5             |
| Spain       | 2005-2015      | 16687/10880587 | 153.4            | 12341/1            |
| 5-9         |                |             |                    |                    |
| Australia   | 2001-2016      | 9146/11398585 | 80.2              | 6402/1             |
| Canada      | 1994-2015      | 7280/21678340 | 33.6              | 5004/1             |
| Finland     | 1995-2016      | 789/3440956  | 23                 | 564/3              |
| Germany     | 2001-2016      | 22704/30760941 | 73.8             | 17873/1            |
| Israel      | 1991-2016      | 5138/7977400 | 64.4               | 3304/1             |
| New Zealand | 1997-2015      | 5161/2899540 | 178                | 3540/1             |
| Spain       | 2005-2015      | 5512/13017097 | 42.3             | 3919/1             |
| 10-14       |                |             |                    |                    |
| Australia   | 2001-2016      | 7816/11377822 | 68.7              | 4080/1             |
| Country    | Start-Year | Cases/(Population Size) | Percentage | Rate |
|------------|------------|-------------------------|------------|------|
| Canada     | 1994-2015  | 5663/22713799           | 25         | 3124/ |
| Finland    | 1995-2016  | 976/3522497             | 27.7       | 633/3:|
| Germany    | 2001-2016  | 24472/33455166          | 73.1       | 15176 |
| Israel     | 1991-2016  | 3822/7398300            | 51.6       | 1720/ |
| New Zealand| 1997-2015  | 4906/2919850            | 168        | 2579/ |
| Spain      | 2005-2015  | 2382/12301238           | 19.4       | 1436/ |
| Australia  | 2001-2016  | 61143/73591102          | 83.1       | 54717 |
| Canada     | (15-39)    | 52598/12661924          | 41.5       | 44735 |
| Finland    | (15-39)    | 19972/18898064          | 105.7      | 18885 |
| Germany    | (15-39)    | 245134/2578954          | 95.1       | 23455 |
| Israel     | (15-39)    | 9426/35538900           | 26.5       | 8129/ |
| New Zealand| (15-39)    | 37402/13546700          | 276.1      | 33501 |
| Spain      | (15-39)    | 4881/110542308          | 4.4        | 3947/ |
| Australia  | 45-64      | 31795/41988401          | 75.7       | 26708 |
| Canada     | (40-59)    | 31090/10058569          | 30.9       | 27041 |
| Finland    | (40-59)    | 15233/16513241          | 92.2       | 12656 |
| Germany    | (40-59)    | 131198/1816981          | 72.2       | 11238 |
| Israel     | (40-59)    | 2708/14322400           | 19         | 2774/ |
| Country     | Years     | Incidence Rate | RR  | CI    |
|-------------|-----------|----------------|------|-------|
| New Zealand | 1997-2015 | 23452/10201030 | 230  | 19708 |
| Spain       | 2005-2015 | 3394/63103755  | 5.4  | 2296/ |
| Australia   | 2001-2016 | 20158/21417772 | 94   |       |
| Canada      | 1994-2015 | 18731/58764646 | 31.9 |       |
| Finland     | 1995-2016 | 5263/11159619  | 47.2 |       |
| Germany     | 2001-2016 | 64640/10801928 | 59.8 |       |
| Israel      | 1991-2016 | 2734/7087900   | 38.6 |
| New Zealand | 1997-2015 | 14760/6302700  | 234.2|
| Spain       | 2005-2015 | 3788/37127234  | 10.2 |

Table 2: Sensitivity analysis of incidence RR’s for each age group, by removing one country at a time

(RR = rate ratio; CI = confidence interval)
| Age group       | RR (CI) | RR (CI) | RR (CI) | RR (CI) | RR (CI) |
|----------------|---------|---------|---------|---------|---------|
| Country Removed |         |         |         |         |         |
| Australia      | -       | -       | 1.35    | 1.69    | 1.1     |
|                |         |         | (1.25-1.45) | (1.53-1.87) | (1.03-1.18) |
| Canada         | 1.31    | 1.33    | 1.34    | 1.71    | 1.1     |
|                | (1.17-1.46) | (1.21-1.46) | (1.25-1.44) | (1.54-1.9) | (1.03-1.16) |
| Finland        | -       | -       | 1.35    | 1.75    | 1.12    |
| Germany        | 1.32    | 1.35    | 1.38    | 1.75    | 1.12    |
|                | (1.18-1.48) | (1.25-1.46) | (1.34-1.42) | (1.62-1.89) | (1.08-1.16) |
| Israel         | 1.24    | 1.28    | 1.33    | 1.65    | 1.1     |
|                | (1.21-1.27) | (1.23-1.34) | (1.25-1.41) | (1.53-1.79) | (1.03-1.17) |
| New Zealand    | 1.3     | 1.33    | 1.34    | 1.69    | 1.1     |
|                | (1.16-1.46) | (1.21-1.45) | (1.25-1.41) | (1.53-1.79) | (1.03-1.17) |
| Spain          | 1.31    | 1.34    | 1.35    | 1.74    | 1.09    |
|                | (1.16-1.49) | (1.22-1.48) | (1.26-1.44) | (1.57-1.87) | (1.03-1.16) |

Declarations

**Ethics approval and consent to participate**

There was no collection of data from individual subjects and no need for ethical approval

**Consent for publication**

There was no use of individual data and no need for consent for publication
Availability of data and materials
All data are available from the original sources or from the authors.

Competing interests
The authors declare that they have no competing interests.

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No funding sources were used for the study.

Authors’ contributions
MSG designed and supervised the study and participated in the analysis and interpretation of the data and in writing the manuscript. NS assisted in the data analysis and contributed important input in the review of the manuscript. VP participated in the study design, collected the data, helped in the interpretation of the analyses and writing the manuscript. All authors approved the final version submitted.

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Authors’ information
MSG is a physician epidemiologist and a professor in the School of Public Health at the University of Haifa. His research interests include individual immune responses to vaccines and sex differences in infectious diseases and the response to vaccines. NS is an epidemiologist and VP is a PhD candidate studying aspects of sex differences in infectious diseases and vaccines under the supervision of MSG.
Figures
Figure 1

Forest plot of the male to female Campylobacter incidence rate ratios (RR) for different years.
Figure 2

Forest plot of the male to female Campylobacter incidence rate ratios (RR) for different years in Canada, Germany, Israel, New Zealand, and Spain in early childhood (ages 1-4).
| Country    | Subtotal (I² = 35.3%, p = 0.147) | 2001-2002 | 2003-2004 | 2005-2006 | 2007-2008 | 2009-2010 | 2011-2012 | 2013-2014 | 2015-2016 |
|------------|----------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Australia  |                                  | 1.21      | 1.23      | 1.35      | 1.37      | 1.39      | 1.43      | 1.31      | 1.30      |
|            |                                  | (1.11, 1.31) | (1.23, 1.48) | (1.25, 1.50) | (1.27, 1.52) | (1.30, 1.57) | (1.19, 1.44) | (1.30, 1.58) | (1.29, 1.50) |
|            |                                  | 2.08      | 2.02      | 2.03      | 2.04      | 2.02      | 1.99      | 1.95      | 2.14      |
|            |                                  | (1.82, 2.36) | (1.80, 2.45) | (1.83, 2.51) | (1.85, 2.60) | (1.86, 2.58) | (1.89, 2.55) | (1.85, 2.58) | (1.90, 2.46) |
| Canada     |                                  | 1.44      | 1.41      | 1.30      | 1.31      | 1.20      | 1.24      | 1.16      | 1.39      |
|            |                                  | (1.32, 1.56) | (1.38, 1.44) | (1.30, 1.41) | (1.35, 1.50) | (1.34, 1.47) | (1.35, 1.55) | (1.35, 1.51) | (1.37, 1.54) |
|            |                                  | 1.51      | 1.94      | 1.80      | 1.85      | 1.87      | 1.39      | 1.95      | 0.79      |
|            |                                  | (1.30, 1.73) | (1.73, 2.11) | (1.68, 2.03) | (1.74, 2.18) | (1.76, 2.25) | (1.71, 2.12) | (1.80, 2.22) | (1.84, 2.20) |
| Finland    |                                  | 1.02      | 0.94      | 0.91      | 1.27      | 1.84      | 1.22      | 1.58      | 1.53      |
|            |                                  | (0.68, 1.55) | (0.49, 1.36) | (0.66, 1.20) | (0.92, 1.76) | (1.44, 2.35) | (0.94, 1.79) | (0.73, 1.33) | (0.88, 1.69) |
|            |                                  | 0.32      | 0.38      | 0.49      | 0.49      | 0.41      | 0.37      | 0.36      | 0.37      |
|            |                                  | (0.24, 0.50) | (0.29, 0.47) | (0.30, 0.50) | (0.32, 0.47) | (0.37, 0.47) | (0.32, 0.48) | (0.30, 0.44) | (0.31, 0.42) |
| Germany    |                                  | 1.20      | 1.20      | 1.21      | 1.22      | 1.18      | 1.15      | 1.16      | 1.12      |
|            |                                  | (1.14, 1.26) | (1.14, 1.27) | (1.15, 1.27) | (1.16, 1.29) | (1.11, 1.25) | (1.10, 1.27) | (1.16, 1.31) | (1.14, 1.30) |
|            |                                  | 2.51      | 2.49      | 2.49      | 2.44      | 2.42      | 2.37      | 2.37      | 3.25      |
|            |                                  | (2.19, 2.85) | (2.19, 2.85) | (2.19, 2.85) | (2.19, 2.85) | (2.19, 2.85) | (2.19, 2.85) | (2.19, 2.85) | (2.19, 2.85) |
| Israel     |                                  | 1.42      | 1.19      | 1.04      | 1.45      | 1.19      | 1.46      | 1.46      | 1.39      |
|            |                                  | (1.05, 1.91) | (1.10, 1.79) | (0.69, 1.58) | (1.11, 1.80) | (1.02, 1.38) | (1.34, 1.84) | (1.42, 1.91) | (1.23, 1.56) |
|            |                                  | 0.55      | 0.65      | 0.31      | 0.65      | 1.14      | 1.14      | 1.30      | 1.67      |
|            |                                  | (0.35, 0.77) | (0.54, 0.77) | (0.35, 0.77) | (0.54, 0.77) | (0.35, 0.77) | (0.35, 0.77) | (0.35, 0.77) | (0.35, 0.77) |
| New Zealand|                                  | 1.33      | 1.36      | 1.31      | 1.50      | 1.38      | 1.26      | 1.28      | 1.39      |
|            |                                  | (1.17, 1.52) | (1.21, 1.53) | (1.17, 1.46) | (1.33, 1.69) | (1.21, 1.58) | (1.26, 1.70) | (1.07, 1.45) | (1.31, 1.47) |
|            |                                  | 1.57      | 1.52      | 1.80      | 1.79      | 1.56      | 1.37      | 1.24      | 0.74      |
|            |                                  | (1.41, 1.74) | (1.36, 1.53) | (1.50, 1.80) | (1.50, 1.80) | (1.66, 1.86) | (1.37, 1.55) | (1.56, 1.82) | (1.56, 1.82) |
| Spain      |                                  | 1.47      | 1.20      | 1.20      | 1.30      | 1.26      | 1.47      | 1.33      | 1.05      |
|            |                                  | (1.29, 1.68) | (1.08, 1.36) | (1.17, 1.41) | (1.13, 1.50) | (1.17, 1.36) | (1.35, 1.81) | (1.24, 1.42) | (1.21, 1.57) |
|            |                                  | 1.55      | 1.00      | 2.02      | 1.48      | 2.23      | 2.07      | 10.95     | 9.05      |
|            |                                  | (1.36, 1.75) | (1.13, 1.51) | (1.29, 1.71) | (1.37, 1.91) | (1.26, 1.76) | (1.35, 1.81) | (1.34, 1.81) | (1.34, 1.81) |
| Overall    |                                  | 1.35      | 1.36      | 1.99      | 2.04      | 2.02      | 1.99      | 1.95      | 2.14      |
|            |                                  | (1.32, 1.39) | (1.36, 1.40) | (1.94, 2.09) | (2.01, 2.15) | (1.99, 2.16) | (1.95, 2.09) | (1.95, 2.14) | (1.95, 2.14) |

**NOTE:** Weights are from random effects analysis.
Figure 3

Forest plot of the male to female Campylobacter incidence rate ratios (RR) for different years in Australia, Canada, Finland, Germany, Israel, New Zealand, and Spain in late childhood (ages 5-9).
Figure 4

Forest plot of the male to female Campylobacter incidence rate ratios (RR) for different years in Australia, Canada, Finland, Germany, Israel, New Zealand, and Spain in puberty (ages 10-14).

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