BRIEF REPORT

# Incidence of Guillain-Barré Syndrome among Patients with *Campylobacter* Infection: A General Practice Research Database Study

**Clarence C. Tam,[1,2] Laura C. Rodrigues,[1] Irene Petersen,[3] Amir Islam,[3] Andrew Hayward,[3] and Sarah J. O'Brien[4]**

[1]Infectious Disease Epidemiology Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, [2]Environmental and Enteric Diseases Department, Health Protection Agency Centre for Infections, and [3]Department of Primary Care and Population Sciences, University College, London, and [4]Division of Medicine and Neuroscience, School of Medicine, University of Manchester, Salford, United Kingdom

**The association between *Campylobacter* infection and subsequent Guillain-Barré syndrome (GBS) has been well documented. To date, however, there exists no direct estimate of the incidence of GBS among patients with *Campylobacter* infection. Using the General Practice Research Database, we estimate the incidence of GBS in a cohort of patients presenting with *Campylobacter* enteritis to be 1.17/1000 person-years, a rate 77 times greater than that in the general population. The probability that an individual who develops *Campylobacter* enteritis will also develop GBS during the subsequent 2-month period is <2/10,000.**

There is considerable evidence regarding the association between *Campylobacter jejuni* infection and subsequent Guillain-Barré syndrome (GBS) [1–4]. Estimates of the incidence of GBS after *Campylobacter* infection are crucial for determining the true burden of disease attributable to this pathogen; however, direct estimates of GBS incidence after *C. jejuni* infection are lacking. McCarthy et al. [5] reported no GBS cases after 3 large outbreaks of *Campylobacter* enteritis affecting ~3000 people. However, outbreaks are not representative events and often result from infection with clonal strains, not all of which may cause GBS. Using a capture-recapture approach in Sweden, McCarthy and Giesecke [6] produced an estimate of 30.4 GBS-related hospitalizations/10,000 reported *Campylobacter* infections; the corresponding GBS incidence in the general population was 0.3/10,000. Applying this incidence figure to the situation in England, we have elsewhere estimated that 14% of GBS cases could be attributable to symptomatic *C. jejuni* infection in the general population [7]. In the present report, we use data from the General Practice Research Database (GPRD), a representative sample of the primary care, or general practice (GP), population in the United Kingdom, to obtain the first direct estimate of the incidence of GBS in a cohort of patients with *Campylobacter* enteritis.

***Materials and methods.*** The data structure of the GPRD has been described elsewhere [8]. In brief, the GPRD consists of >700 GP clinics serving a representative sample of ~5% of the UK population [8]. Electronic records of all consultations, diagnoses, preventive interventions, and prescriptions are available. Participating clinics provide data fulfilling minimum-quality criteria (i.e., "up-to-standard" [UTS] data). An individual's UTS follow-up time is defined as the time during which he or she is registered with a clinic reporting UTS data. We applied standard survival-analysis techniques to GPRD data from the years 1991–2001, to estimate the incidence of GBS during the 60-day period after development of *Campylobacter* enteritis. Approval for the study was obtained from the scientific and ethics advisory group of the GPRD.

Diagnoses included in the GPRD are recorded by use of Read or Oxford Medical Information Systems (Oxmis) codes. Records of all first consultations between 1 January 1991 and 31 December 2001 that were specific for *Campylobacter* enteritis were abstracted from the GPRD. Repeat consultations with the same patient were excluded, because it is difficult to determine which of these might represent a new episode. We excluded consultations with patients for whom <1 year of UTS data were available. We also excluded consultations made ⩽120 days after the initial registration with the clinic [9], as well as those for which *Campylobacter* enteritis was diagnosed on the same day as a "new patient screening," so as to avoid inclusion of past episodes ascertained when the patient first registered with the clinic. Finally, we excluded patients for whom the follow-up time, either because of transfer out of the clinic or death, was incomplete (i.e., ⩽60 days).

For patients with a first consultation for *Campylobacter* enteritis, we obtained all subsequent episodes of GBS occurring ⩽60 days after initial consultation for *Campylobacter* enteritis.

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Reprints or correspondence: Dr. Clarence C. Tam, Infectious Disease Epidemiology Unit, Dept. of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, United Kingdom (clarence.tam@lshtm.ac.uk).

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Multiple consultations for the same patient were excluded. We avoided inclusion of prevalent GBS by excluding any diagnosis made either ⩽120 days after initial registration with the GP clinic or on the same day as a new patient screening.

The follow-up period for patients with *Campylobacter* enteritis was from the date of consultation for this condition until either their first consultation for GBS or the end of the exposure period, whichever was earliest. The incidence of GBS after development of *Campylobacter* enteritis was defined as the number of consultations for GBS during the subsequent 60-day period divided by the total eligible person-time of follow-up for the patients with *Campylobacter* enteritis.

We obtained, for the same time period, both the total number of first consultations for GBS and the total person-time of follow-up in the GPRD, to estimate the baseline incidence of GBS in the entire GPRD cohort. The ratio of the incidence of GBS in the cohort of patients with *Campylobacter* enteritis to that in the entire GPRD cohort is the relative risk for the association between *Campylobacter* enteritis and subsequent GBS.

All analyses were performed by use of Stata (version 8.0; Stata).

***Results.*** During the study period, there were 15,587 first consultations for *Campylobacter* enteritis, contributing a total of 2560 person-years of follow-up. During the follow-up period, 3 GBS cases occurred among patients with *Campylobacter* enteritis, yielding an incidence of 1.17/1000 person-years (95% confidence interval [CI], 0.38–3.63). The risk of GBS is believed to be elevated for only ~2 months after development of *Campylobacter* enteritis; this incidence thus equates to a <2/10,000 probability that a patient with *Campylobacter* enteritis will develop GBS.

During the study period, the entire GPRD cohort included a total of 551 patients with a first diagnosis of GBS. The median age of these 551 patients was 52.3 years (interquartile range, 33.1–66.2 years), and 313 (56.8%) of them were men. Of these 551 patients, 272 were known to have been hospitalized; no information regarding hospitalization was available for the remaining 279. During the study period, the person-time at risk of GBS in the entire GPRD cohort was 36,300,000 person-years, resulting in a crude incidence of 0.015 GBS cases/1000 person-years (95% CI, 0.014–0.017); the excess risk of GBS among those with *Campylobacter* enteritis was 77.2 (95% CI, 15.9–226.8).

***Discussion.*** We have presented here the first direct estimate of the incidence of GBS in a representative cohort of patients with *Campylobacter* enteritis who have been identified at the GP level; we have estimated this incidence to be ~1/1000 person-years, equating to a probability of <2/10,000 that a patient who develops *Campylobacter* enteritis will also develop GBS during the subsequent 2 months; this represents a 77-fold-greater risk than that in the general population.

Our estimates do not take into account other factors that may influence or modify risk of GBS after development of *Campylobacter* infection—factors such age and/or sex and the virulence of the infecting strain. Because of the small number of GBS cases in our cohort of patients with *Campylobacter* enteritis, it was not possible to obtain estimates stratified by age and sex, and information on *Campylobacter* strains was not available. The present study included only symptomatic *Campylobacter* infections and therefore could not address the issue of development of GBS resulting from asymptomatic *Campylobacter* infection; nevertheless, the results show that the incidence of *Campylobacter*-associated GBS is far from negligible, particularly when it is considered in light of the relatively high incidence of *Campylobacter* infection. The incidence estimated in the present study is slightly lower than that which McCarthy and Giesecke [6] have reported in a study of Sweden. Differences between the populations and/or the distributions of *Campylobacter* strains in the 2 settings might account for this disparity: the Swedish study detected hospitalizations for GBS among *Campylobacter*-enteritis cases reported in national surveillance, and such *Campylobacter*-enteritis cases are likely to represent cases that are more severe than those presenting to GP clinics; a higher incidence of GBS might be expected if more-severe *Campylobacter* enteritis is associated with an increased risk of GBS. Using the Swedish incidence data, we have elsewhere estimated that ~14% of all admissions for GBS could be attributable to symptomatic *C. jejuni* infection in the general population [7]. If the incidence estimated by the present study is applied to the data in our earlier study, an estimated 104 *Campylobacter*-associated GBS cases can be expected to occur in England every year, representing 9% of all hospitalizations for GBS; this figure is lower than that suggested by some serological studies, in which the prevalence of *C. jejuni* infection among GBS cases has been reported to be 13%–72% [10]. Serological studies are likely to detect asymptomatic infection, which might partly account for this difference. However, the results of such studies are difficult to interpret, because it has been shown that, after development of *C. jejuni* infection, antibody levels can remain high for several months and perhaps even years [11]. Serological assays are not specific for recent *C. jejuni* infection and therefore are likely to provide biased estimates of the proportion of GBS cases attributable to this pathogen.

Studies estimating the incidence of GBS commonly use hospitalization data to determine the number of GBS cases [12–16]. It is commonly assumed that, because the condition is potentially life threatening, most such patients are hospitalized—and that hospitalization data therefore are likely to identify the vast majority of GBS cases; unfortunately, GPRD data contain limited information on hospitalization, and we could not test this assumption in this study because information on hospitalization was available for only approximately half of the GBS cases. A GP–based study that reviewed medical records of GBS

cases would be helpful in this respect, because this issue has important implications for the population-wide surveillance of GBS.

The findings of the present study emphasize *Campylobacter*'s role as a major causative agent of GBS. The health impact of *Campylobacter*-related GBS, as well as other sequelae, such as reactive arthritis, is considerable; studies of the burden imposed by *Campylobacter* infection should take into account these indirect effects, as well as those arising from primary infection, to obtain a more comprehensive picture of both the morbidity caused by this pathogen and the potential impact that strategies for its control might have. Such studies will be dependent on reliable estimates of the incidence of *Campylobacter*-associated complications, and further such studies are required. Although the incidence of these complications may be low, the high incidence of *Campylobacter* infection means that, at the population level, they can have a substantial impact. Our analyses using GPRD data indicate that strategies to control *Campylobacter* infection in the general population will be key to the reduction of morbidity due to GBS, now the most common cause of acute flaccid paralysis in polio-free regions.

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