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SHORT REPORT
Increased incidence of *Campylobacter jejuni*-associated Guillain–Barré syndromes in the Greater Paris area

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SUMMARY

The role of *Campylobacter jejuni* as the triggering agent of Guillain–Barré syndrome (GBS) has not been reassessed since the end of the 1990s in France. We report that the number of *C. jejuni*-related GBS cases increased continuously between 1996 and 2007 in the Paris region (mean annual increment: 7%, $P = 0{\cdot}007$).

Key words: Guillain–Barré syndrome, Miller–Fisher syndrome, *Campylobacter jejuni*, *Campylobacter*.

Guillain–Barré syndrome (GBS) is a post-infectious neurological disease characterized by acute-onset flaccid paralysis. Its estimated median annual incidence in developed countries is 1·3/100 000 inhabitants [1]. *Campylobacter jejuni* is the most frequent triggering agent, and is associated with particularly severe forms of the disease and a high prevalence of long-term motor sequelae [2, 3]. Several large studies evaluated the causal role of *C. jejuni* in GBS in Western Europe, and reported prevalence rates of around 20–30% [2–5]. The incidence of *C. jejuni*-associated GBS has also been reported to be higher in the summer months [6]. However, these findings are mostly based on data collected in the early 1990s. Indeed, little information is available concerning the current role of *C. jejuni* in GBS in Western Europe, or any changes that may have occurred since the mid-1990s. In a previous study using serology, bacteriological culture and real-time PCR, we provided evidence that *C. jejuni* was a major GBS triggering agent in France [7]; this study also confirmed the good sensitivity of serology to detect a recent *C. jejuni* infection in this setting [2, 7], making this approach particularly suitable for epidemiological surveys of *C. jejuni*-associated GBS [2]. We report herein the data from a large prospective cohort of GBS cases in the Greater Paris area between 1996 and 2007.

The medical intensive care unit of the Raymond Poincaré hospital (Garches, France) is a reference centre for the management of adult patients with GBS in the Greater Paris area. The study population included all patients with GBS or Miller–Fisher syndrome (MFS), who were admitted between 1996 and

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2007, and for whom pre-treatment sera were available. Participating patients were followed prospectively for 12 months as previously described [5, 7–9]. Data were managed in accordance with French law ('Loi informatique et liberté'; Loi 78-17).

Pre-treatment serum samples were assayed for antibodies against *C. jejuni* with the complement fixation test (CFT; Virion\Serion, Germany). We used a cut-off titre of $\geqslant 20$, which provides a specificity of >95% (Virion\Serion) and a sensitivity of 93·5% (i.e. the CFT titre $\geqslant 20$ for 93·5% of *C. jejuni*-associated GBS cases identified by culture of the organism from stools) [7]; the specificity provided with this cut-off was confirmed to be >95% (96·1%) by screening a panel of 76 serum samples collected in 2007 from 76 healthy blood donors living in the Greater Paris area (this study). Other laboratory tests performed included the detection of antibodies against cytomegalovirus (CMV), Epstein–Barr virus and *Mycoplasma pneumoniae*, and assays for anti-GM1 antibodies [9].

Monthly reports of *C. jejuni* isolations from enteritis cases in the Greater Paris area were obtained through the national Campylobacter surveillance network. Fully operational since 2003, this surveillance system is based on a voluntary network of private and public laboratories that send their *Campylobacter* isolates to the National Reference Centre (NRC) for *Campylobacter* and *Helicobacter*. About 25% of public laboratories and 8–9% of private laboratories participated in this network during the study period (9–11% of all French laboratories), with an increase in the proportion of participating public laboratories between 2003 and 2007 (from 20% to 28–29%, $P<0·05$).

Statistical analyses were performed with R 2.10.1 software (R Foundation for Statistical Computing, Austria). Categorical variables were compared using Fisher's exact tests, and quantitative variables were compared using Wilcoxon tests. All tests were two-sided, and $P<0·05$ values were considered significant. Seasonal trends in cases (or *C. jejuni* isolation) were analysed by the method of Jones *et al*. [10], which is based on a Poisson model for case incidence, with a potential linear trend in time and several harmonics for the seasonal pattern. The number of harmonics (seasonality periods) was determined using Akaike's Information Criterion (AIC).

A total of 561 cases of GBS (or MFS) were admitted between 1996 and 2007. Four cases were excluded from the study because no pre-treatment serum was available and we thus included 557 cases. There was serological evidence of recent infection with *C. jejuni* for 153 (27·5%) cases (median CFT titre 80, interquartile range 40–320); two of these cases also had evidence of primary CMV infection and were excluded from the analysis. The mean (S.D.) age of *C. jejuni*-associated GBS cases ($n=151$) was 51·5 (17·9) years. They differed significantly from *C. jejuni*-negative GBS cases ($n=404$): *C. jejuni*-associated GBS cases were more likely to be male (66·2% *vs.* 54·2%, $P=0·012$), to have prodromal diarrhoea (46·4% *vs.* 12·9%, $P<0·0001$), to have a pure motor GBS form (57·3% *vs.* 31·0%, $P<0·0001$) or MFS (4·0% *vs.* 0·5%, $P=0·006$), to have anti-GM1 antibodies (32·7% *vs.* 3·9%, $P<0·0001$) and to have severe long-term sequelae (14·7% *vs.* 4·8%, $P=0·0015$). Similar data were found for cases admitted in the period 1996–2001 and those admitted in the period 2002–2007 (not shown).

We analysed the temporal variations in the incidence of cases included during the study period. The monthly number of GBS cases as a whole did not show a significant time trend between 1996 and 2007 ($P=0·18$), with a mean of 3·9 cases (S.D. = 1·9) per month (Fig. 1*a*). By contrast, the monthly number of *C. jejuni*-associated GBS cases increased significantly during this period, by a mean of 7% per year (95% confidence interval 2–12, $P=0·007$) (Fig. 1*b*).

No time trend was found for *C. jejuni*-negative GBS cases ($P=0·92$), with an average of 2·8 cases (S.D. = 1·7) per month (Fig. 1*c*). We did not find significant seasonal patterns for the included GBS cases as a whole or for the subgroup of *C. jejuni*-negative cases (Fig. 1*a*, *c*). By contrast, a significant seasonal component was found for *C. jejuni*-associated GBS cases ($P=0·019$): there were peaks in incidence in May and November, such that there was a cycle with a 6-month period (Fig. 1*b*).

Our data were compared to those obtained through the national *Campylobacter* surveillance network for the Greater Paris area and for the rest of France. The number of *C. jejuni* isolations from enteritis cases per year increased significantly between 2003 and 2007 for both the Greater Paris area (mean 4% per year, $P=0·032$) and for the rest of France (mean 12% per year, $P<0·0001$) (data not shown); the rate of increase was significantly higher for the rest of France than in Greater Paris ($P=0·0006$). Seasonal patterns also differed between the Greater Paris area (where the distribution of isolations was even throughout the year with only minor peaks in February, June and September) and the rest of France (major peak in July) ($P<0·0001$).

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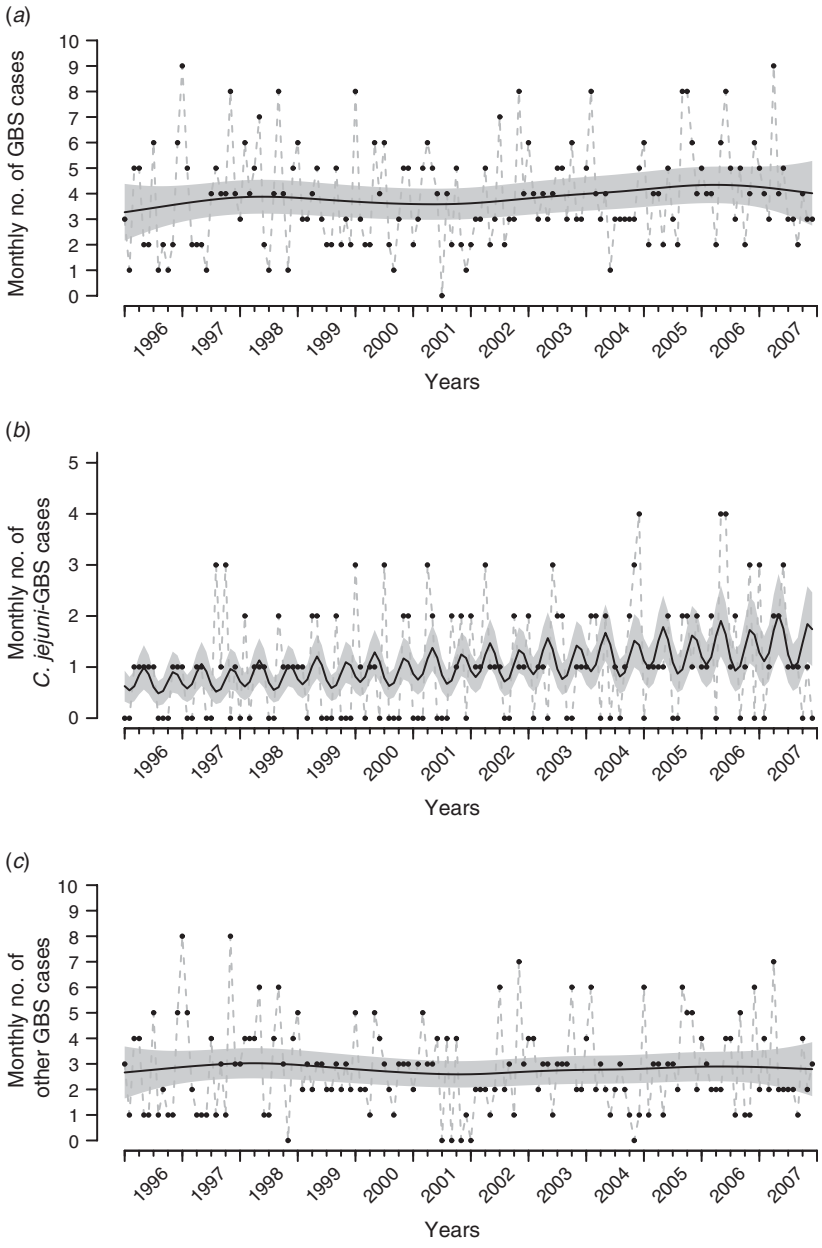

Fig. 1. Monthly numbers of Guillain–Barré syndrome (GBS) cases admitted to the centre between 1996 and 2007. (*a*) All GBS cases. (*b*) *C. jejuni*-associated GBS cases. (*c*) *C. jejuni*-negative GBS cases. The thick lines in panels (*a*) and (*c*) represent the prediction from generalized additive Poisson modelling, and the grey shaded areas indicate the 95% confidence intervals. Panel (*b*) displays the seasonal Poisson predictions with their 95% confidence intervals.

Our data show an increase in the prevalence of *C. jejuni*-associated GBS in the Greater Paris area between 1996 and 2007. The increase was 7% per year, which is substantially greater than the increase in the population over the same period (0·6% per year) (http://www.recensement.insee.fr/). The observed increase is unlikely to have resulted from recruitment bias, although this possibility cannot be formally excluded. In particular, there was no evidence of any relative increase in referral to our centre of more severely affected cases, which are more likely to be associated with *C. jejuni* infection [2]. We found instead that the proportion of patients requiring mechanical ventilation had tended to decrease between the first (1996–2001) and the second (2002–2007) half of the study period (mean 33% *vs.* 26%, $P=0{\cdot}078$). It is also noteworthy that the number of *C. jejuni*-associated GBS patients has increased with no

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detectable change over time in the characteristics of the patients (mostly men between the ages of 50 and 60 years, as in previous series). Similarly, we found no change over time in the clinical characteristics, which were typical of those generally reported (i.e. particular frequency of prodromal diarrhoea, pure motor form and anti-GM1) [2, 3, 5]. Thus, the serology-based approach used here allowed the detection of 'true' *C. jejuni*-associated GBS cases.

We observed peaks in the incidence of *C. jejuni*-associated GBS in May and November, but no peak during the summer. This apparently novel pattern may be a consequence of changes in the epidemiology of *C. jejuni*-associated enteritis; this is consistent with data from the national *Campylobacter* surveillance network, although a limitation of our study is that the *Campylobacter* surveillance network relies on the data from only 10% of the laboratories in the area. Indeed, this network has revealed an increase in the incidence of *C. jejuni*-associated enteritis, similar to that we report for *C. jejuni*-associated GBS. However, the *Campylobacter* surveillance network data show that there is a difference between the Greater Paris region and the rest of France: for France as a whole, *C. jejuni* is most frequently isolated in June, July and August, whereas in the Greater Paris region, the distribution is more even throughout the year, without the summer peaks typically observed in Western Europe [11] but with smaller peaks in February, May and September. Unfortunately, we cannot determine whether this is only a recent phenomenon, because the national *Campylobacter* surveillance network was not fully operational before 2003.

Altogether, these findings suggest that there have recently been changes in the epidemiology of *C. jejuni*-associated GBS, and very probably *C. jejuni* infection, in the Paris region. The causes are unclear. *C. jejuni* enteritis is mainly a foodborne disease [12, 13], so these changes may be due to developments in eating and associated behaviours: changes in food conservation, preparation and cooking methods, and increases in the number of meals eaten outside the home [13]. They also may be due, at least partially, to a greater proportion of cases being epidemic. The overall epidemiology of *Campylobacter* infections in the USA shows a higher proportion of cases between May and November, with a peak in August/September [14, 15]. Interestingly, epidemiological investigations in the 1980s found that outbreak-associated cases of *C. jejuni* infection peak in May and October, a seasonal pattern very similar to that we describe [14]; however, a more recent study reported similar seasonal patterns for outbreak-associated and sporadic cases (i.e. peaks in May and June) [15].

A major limitation of this study is the relatively small number of cases included. It is therefore difficult to draw firm conclusions from our data. However, although the underlying causes are not necessarily the same, data similar to ours were recently reported by a study in New Zealand. The New Zealand study used a different approach based on the analysis of rates of GBS hospitalization and campylobacteriosis – a notifiable disease since 1980 in New Zealand [16]. These authors show that the national incidence of GBS hospitalizations and of campylobacteriosis notifications increased continuously between 1988 and 2006, such that these values were abnormally high between 2003 and 2006. In 2006, in response to this situation, New Zealand introduced a series of measures aimed at reducing the contamination of poultry by *Campylobacter*. This was followed by a 50% decrease of campylobacteriosis notifications and a 13% decrease of hospitalizations for GBS in 2008–2010.

The epidemiology of GBS reflects that of the agents that can cause this disease, and is therefore likely to change through time. We recently found that the proportion of GBS cases associated with CMV – the second most prevalent agent causing GBS – has decreased over the last 10 years [9]. We have also shown that flu-associated GBS cases are only observed in seasons in which there is a major flu epidemic [8]. GBS associated with *C. jejuni* is similarly subject to changes through time, as illustrated by the New Zealand study based on analyses of national data [16]. Our data, similarly, suggest fluctuations through time, but need to be confirmed by further studies involving larger numbers of cases.

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DECLARATION OF INTEREST

None.

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