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Guillain-Barré syndrome (GBS) is a rare but serious complication of infectious intestinal disease due to Campylobacter jejuni. To date, estimates of the burden of C. jejuni-associated GBS have been based on limited data regarding the proportion of GBS attributable to this pathogen. In this paper, we combine data obtained from Sweden and a large study of infectious intestinal disease with routine and surveillance data from England to estimate the number and proportion of GBS cases attributable to C. jejuni. We estimate that, between 1 April 2000 and 31 March 2001, symptomatic C. jejuni infection was responsible for 157 cases of GBS, constituting approximately 15% of all GBS cases in England.

Following the successful control and elimination of polio in many regions of the world, Guillain-Barré syndrome (GBS) has become the most common cause of acute neuromuscular paralysis, with estimates of the annual incidence ranging from 0.4 to 4.0 cases per 100,000 individuals in different populations [1]. The majority of cases appear to have an infectious trigger, and the most commonly reported of these triggers is Campylobacter jejuni infection. The first case of Campylobacter-associated GBS was reported in 1982. Since then, numerous epidemiologic studies have provided additional evidence linking campylobacter infection to GBS and Miller Fisher syndrome (MFS), a related illness [2–5]. Patients with GBS and evidence of a prior campylobacter infection have been shown to experience slower recovery and poorer outcome from GBS after 1 year [5], and studies in 2 countries have found a link between GBS and particular C. jejuni serotypes, namely, O:19 in Japan and O:41 in South Africa [6, 7]. The disease is thought to have an autoimmune mechanism that involves the production of antibodies against C. jejuni surface molecules with a structural similarity to ganglioside antigens on nerve endings [8].

Estimates of the incidence of Campylobacter-associated GBS are important for studies of the health and economic burden of infectious intestinal disease (IID) due to C. jejuni. Such estimates require knowledge of the incidence of GBS occurring after infection with C. jejuni. Prospective follow-up studies to obtain a direct estimate are not very efficient, because only a small proportion of all patients with C. jejuni IID undergo laboratory investigation, and GBS is a relatively rare complication. Previous estimates of the incidence of GBS have ranged from 20 to 95 GBS cases per 100,000 cases of C. jejuni IID [9, 10]. However, these estimates were based on assumptions about the proportion of GBS cases attributable to C. jejuni infection, for which no reliable data are available. Case-control studies to determine the proportion of GBS cases attributable to C. jejuni have generally relied on the results of serological assays to diagnose recent C. jejuni infection, because, by the time a patient develops neurological symptoms, the patient may no longer excrete the organism in the stool. The lack of a standard serological assay for C. jejuni, however, makes the results of such studies difficult to compare. There is also evidence to suggest that, following C. jejuni infection, antibody levels may remain elevated even after 12 months, particularly those of the IgG isotype [11, 12], which has often been used as part of the diagnostic criteria in such studies [3–5]. More importantly, the correlates of immunity to C. jejuni are currently poorly understood. A positive serological test result for a control patient without GBS is thus difficult to interpret, because it could be indicative of recent C. jejuni infection, C. jejuni infection some time ago, or immunity to C. jejuni infection. This brings into question the comparability of patients with GBS and the control patients without GBS in terms of their exposure to C. jejuni infection as determined by the results of serologic testing.

Estimates of the proportion of GBS cases attributable to C. jejuni infection based on data for cases of GBS arising from outbreaks of C. jejuni IID have also been reported [13], but these are unlikely to be representative; outbreaks are caused by clonal isolates, whose propensity for causing GBS may vary. Using an alternative approach, McCarthy and Giesecke [14] linked laboratory reports of C. jejuni infection with cases of GBS identified through the Swedish Inpatient Register. This capture-recapture approach yielded an estimate of 30.1 cases...
of GBS per 100,000 cases of laboratory-confirmed C. jejuni IID in Sweden. The study identified 9 cases of GBS among individuals with reported C. jejuni IID over an 8-year period. This number—9 cases in 8 years—is likely to be a gross underestimate, because only a small minority of C. jejuni IID cases are reported to national surveillance [15]. In this article, we extend the Swedish method to estimate the number and proportion of GBS cases attributable to both reported and unreported C. jejuni in England, using data on the degree of under-ascertainment of C. jejuni IID in the community from a large study of IID in England and data from the Hospital Episodes Statistics database [16] and routine surveillance.

Methods. The incidence of GBS following identified C. jejuni IID was taken from the study by McCarthy and Giesecke [14] in Sweden. In that study, the authors estimated the incidence of GBS among a cohort of patients with laboratory-confirmed C. jejuni IID reported to the Swedish Institute for Infectious Disease Control. They did so by linking patients’ national personal identifier to data on patients with GBS recorded in the Swedish Inpatient Register for the 2-month risk period following infection. They reported an estimate of 30.1 GBS cases per 100,000 laboratory reports of C. jejuni IID.

Because Campylobacter isolates are not routinely speciated by microbiology laboratories, the number of reported cases of C. jejuni infection cannot be determined directly from laboratory reports. Data from a sentinel surveillance scheme of Campylobacter infection in England and Wales indicate that ~92% of Campylobacter species isolates from humans C. jejuni [17]. The number of reported cases of C. jejuni infection in England between 1 April 2000 and 31 March 2001 was estimated by multiplying the number of laboratory reports of Campylobacter species by 92% (Appendix, Step 1).

To account for under-ascertainment of C. jejuni IID by national surveillance, a correction factor of 10.3 was applied (Appendix, Step 2). This was derived from the study of IID in England, which estimated that for every 1 case of campylobacter IID reported to national surveillance, 10.3 cases occur in the community [15].

The expected number of GBS cases associated with reported C. jejuni IID was derived by applying the Swedish estimate of C. jejuni-associated GBS incidence to the number of laboratory reports for C. jejuni (Appendix, Step 3). This same incidence was then applied to the number of C. jejuni IID cases in the community to obtain the total expected number of GBS cases associated with C. jejuni IID (both reported and unreported), assuming equal incidences of GBS among reported and among unreported C. jejuni IID cases (Appendix, Step 5).

Data on the number of new hospital admissions in the 12-month period between 1 April 2000 and 31 March 2001 were obtained from the Hospital Episodes Statistics database [16], which collects information on in-patient episodes of healthcare provided by National Health Service (NHS) hospitals in England. The number of new hospitalizations occurring within the specified period was obtained for code G61.0 (inflammatory polyneuropathy Guillain-Barré syndrome) of the International Classification of Diseases, Tenth Revision (ICD-10).

The proportion of GBS cases attributable to reported and unreported C. jejuni IID (i.e. the population-attributable fraction, or PAF) was obtained by dividing, respectively, the expected number of C. jejuni laboratory reports and community cases associated with GBS by the total number of GBS cases identified in the Hospital Episodes Statistics database [16] (Appendix, Steps 4 and 6).

Results. Considering only cases of C. jejuni IID that were reported to national surveillance, and assuming an incidence of subsequent GBS in these cases of 30.1 per 100,000, we estimated that from 1 April 2000 to 31 March 2001, 15 GBS-related hospital admissions were attributable to C. jejuni IID. GBS cases associated with reported C. jejuni IID constituted 1.3% of all GBS cases (Appendix, Step 4).

When both reported and unreported cases were considered, the total expected number of GBS-related hospitalizations due to all C. jejuni IID cases in the community for the 12-month period was 157, corresponding to a population attributable fraction of 13.7% (Appendix, Step 6).

Discussion. We have estimated that symptomatic infection with C. jejuni gives rise to $>150$ GBS cases per year, accounting for ~15% of all GBS-related hospitalizations (Appendix, Step 5).

In obtaining our estimate, we have assumed that the risk that GBS will develop in a patient with C. jejuni IID reported to national surveillance in England is the same as that in Sweden and that the reporting pyramid for C. jejuni is similar in both countries. The 2 countries are likely to be similar with respect to the ascertainment of gastrointestinal pathogens, although, to our knowledge, no study to determine reporting pyramids for specific organisms has been carried out in Sweden, and no direct comparison with the English system can be made to validate this assumption. The risk of GBS following C. jejuni infection is likely to be stable between the 2 countries, but could be influenced by differences in the distribution of C. jejuni strains (because some strains may be more likely to cause GBS than others) and possibly by certain genetic factors in the host. Knowledge of strain-specific differences in incidence or relevant host genotypes is, however, currently lacking.

In estimating the number of GBS cases attributable to all symptomatic C. jejuni infections, we assumed that the incidence of GBS was the same among reported and unreported cases of C. jejuni IID. The major difference between reported and unreported cases of IID is the severity of the disease [18]. However, little is known about whether there is a relationship between

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the severity of C. jejuni IID and the likelihood of developing GBS. If such a relationship exists, the incidence of GBS among unreported cases of C. jejuni IID could differ from that of reported cases, and our assumption that the incidence of GBS was the same among reported and unreported cases of C. jejuni IID might not be valid.

In this analysis, we have not taken into account cases of GBS arising from asymptomatic C. jejuni infection. Evidence of C. jejuni infection in patients with GBS who have no history of recent diarrheal illness has been previously reported [19]. It is not clear whether such individuals share the same risk of developing GBS as those with symptomatic C. jejuni infection.

A further limitation of our estimate is that HES data do not include episodes among in-patients at private hospitals. This may have resulted in an underestimate of the total number of GBS cases. Given the relative rarity of GBS and the universality of NHS care in England, however, it is unlikely that this would make a substantial difference in our estimate. In addition, a number of cases of GBS may be classified under alternative ICD-10 codes, namely G61.9 (inflammatory polyneuropathy unspecified). A review of patient records would be necessary to determine the degree of misclassification.

Although our analysis shows that C. jejuni IID gives rise to a relatively small number of GBS cases, those cases are nonetheless likely to result in a considerable contribution to the health burden attributable to GBS. Patients with GBS spent a median of 14 days in the hospital during the study period, and there is evidence to suggest that having had a prior C. jejuni infection results in a more severe course of GBS, with patients being more likely to require mechanical ventilation [2] and more likely to experience longer and more severe periods of disability [20, 21]. The economic and societal costs of C. jejuni-associated GBS are, therefore, likely to be substantial. A study of the health burden due to Campylobacter species in The Netherlands estimated that this organism accounted for 1382 disability adjusted life years annually, of which 376 resulted from GBS [9]. In the United States, Buzby et al. [22] estimated the annual cost of Campylobacter-associated GBS at between US$ 0.2 and 1.8 billion in direct medical costs and lost productivity. To date, however, such estimates have been based on limited data on the incidence and proportion of GBS due to C. jejuni infection. The IID study in England estimated the average cost of a case of Campylobacter IID in medical and direct patient costs at UK£ 314 (1995 prices), but did not include costs due to GBS [15]. The true cost of Campylobacter IID is, therefore, far from clear. In particular, our analysis shows that the actual burden of C. jejuni-associated GBS could be up to 10 times greater than that estimated through reported cases of Campylobacter IID alone. The estimates of the incidence of C. jejuni-associated GBS presented here should help guide future assessments of the overall burden of this major human pathogen.

APPENDIX

Step 1. The number of laboratory reports of cases of C. jejuni IID in England between 1 April 2000 and 31 March 2001 was estimated using the formula \( L_{ij} = L_{app} \times P_{jejuni} \), where \( L_{ij} \) is the estimated number of laboratory reports of C. jejuni IID in England during this period, \( L_{app} \) is the number of laboratory reports of Campylobacter species isolation in England in this period (from the National Database for Laboratory Confirmed Infections [LabBase]), and \( P_{jejuni} \) is the proportion of cases of Campylobacter infection due to C. jejuni (from [17]). We determined that \( L_{app} \) was 54,990, \( P_{jejuni} \) was 91.9%, and the \( L_{ij} \) estimate was 50,536.

Step 2. The total number of cases of C. jejuni IID in England (reported and unreported) between 1 April 2000 and 31 March 2001 was estimated using the formula \( C = L_{jejuni} \times AR \), where \( C \) is the estimated number of cases of C. jejuni IID (reported and unreported) in England during that period and \( AR \) is the ascertainment ratio (the ratio of cases of Campylobacter IID in the community to reported cases [from 15]). We determined that \( L_{jejuni} \) was 50,536, \( AR \) was 10.3, and \( C \) was 520,519.

Step 3. The number of GBS hospital admissions associated with reported C. jejuni IID in England between 1 April 2000 and 31 March 2001 was estimated using the formula \( H_{i} = L_{jejuni} \times i \), where \( H_{i} \) is the estimated number of GBS hospital admissions associated with reported C. jejuni IID in England during that period and \( i \) is incidence of GBS following reported C. jejuni IID in Sweden (from [14]). We determined that \( L_{jejuni} \) was 50,536, \( i \) was 30.1/100,000, and \( H_{i} \) was 15.

Step 4. The percentage of GBS cases attributable to reported C. jejuni IID was estimated using the formula \( g_{e} = H_{e} / G \times 100\% \), where \( g_{e} \) is the percentage of GBS cases attributable to reported C. jejuni IID and \( G \) is the number of hospital admissions for GBS in England between 1 April 2000 and 31 March 2001 (from Hospital Episodes Statistics [16]). We determined that \( H_{e} \) was 15, \( G \) was 1144, and \( g_{e} \) was 1.3%.

Step 5. The number of GBS hospital admissions due to all C. jejuni IID in England (reported and unreported) between 1 April 2000 and 31 March 2001 was estimated using the formula \( H_{i} = C \times i \), where \( H_{i} \) is the estimated number of GBS hospital admissions due to all C. jejuni IID in England (reported and unreported) during that period. We determined that \( C \) was 320,519, \( i \) was 30.1/100,000, and \( H_{i} \) was 157.

Step 6. The percentage of GBS cases attributable to all C. jejuni IID (reported and unreported) was estimated using the formula \( g_{e} = H_{e} / G \times 100\% \), where \( g_{e} \) is the percentage of GBS hospital admissions due to all C. jejuni IID in England (reported and unreported) during that period.
cases due to all cases of C. jejuni IID (reported and unreported). We determined that $H$ was 157, $G$ was 1144, and $g$ was 13.7%.

References