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Reply: Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome

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Reply to Correspondence: Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome

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We were pleased to receive the correspondence from colleagues in relation to our publication in Brain that found no demonstrable causal association between COVID-19 infection and GBS in the UK in the first 6 months of 2020.(1) We are grateful for the chance to clarify some of the important and relevant issues raised by them.

Our published paper used several methodologies including an epidemiological cohort, a phenotypic cohort, geographical profiling, national COVID and GBS statistics and exploratory molecular characterisation studies to try to determine any relationship of COVID-19 to GBS. The information from each of these individual parts has acknowledged deficiencies, but they should be considered as a whole. We found no association between GBS and COVID-19, and updated epidemiological data from the second wave presented below further support this. This lack of association between GBS and COVID-19 should reassure us, and the world's population, of the anticipated safety of the COVID-19 vaccines in relation to GBS; we think it very unlikely that COVID-19 vaccines would cause GBS any more than by chance alone (2).

Foschi *et al*. {letter of correspondence} and Vogrig *et al*. {letter of correspondence} have not understood our use of the epidemiological and the phenotypic cohorts in the manner we intended. These two parts of our paper must be considered separately, but collectively add weight to our conclusion. The phenotyped population of 47 patients registered in our survey by knowledgeable British Peripheral Nerve Society members undoubtedly collected a non-random sample and thus high number of patients with COVID-19. This disproportionate population of GBS cases with COVID-19 (53%) was collated to better understand whether any specific phenotypic disease characteristics differentiated GBS from GBS associated with COVID-19. We did not intend to imply that 53% was the rate of COVID-19 in patients who developed GBS during the pandemic. Any incidence calculations from this cohort would be inaccurate because of the selection bias.

The UK-wide National Immunoglobulin Database (https://igd.mdsas.com) on which our epidemiological cohort is based captures all hospitalised cases of GBS considered for, or receiving, IVIg (the standard treatment used in 90% of hospitalised GBS in the UK) and thus generates a reliable incidence of GBS within reported ranges (3). We therefore considered it an ideal source to count the most accurate possible total number of GBS cases that occurred during the pandemic period in question, and allowed us to compare this to the cumulative rates and geographical occurrence of COVID-19 infection.

Del Castillo, Foschi and Vogrig all commented on our observed reduction in total GBS cases in the UK in the first half of 2020 {refs to letters of correspondence}. They reiterate several of the possible explanations we considered in our paper, principally that lockdown measures, including social distancing, improved hand hygiene and wearing of masks, have probably reduced the community circulation of *Campylobacter jejuni* and other known infectious precipitants of GBS, thereby creating an inverse peak in GBS that obscured any COVID-19 infection-associated GBS. The second wave of COVID has given us the opportunity to watch the effect of a massive realised increase in COVID-19 infections (see below) which has not been associated with any further changes in the hygiene and distancing measures already in place from wave 1. Thus, arguments for a falling baseline from environmental confounders are weakened. No discernibly significant increase in UK GBS cases requiring IVIG treatment has occurred in the last quarter of 2020 (figure 1).

The detected Covid-19 infections are mainly the 20% of the population who are symptomatic and thus tested, but they provide us with a comprehensive cohort in which to quantitate the expected increase in GBS associated with the UK 2nd wave. Del Castillo *et al.* compare our data to their series of 21 patients from 61 emergency departments in Spain (4), and the two series of Filosto *et al.* (34 patients) and Gigli *et al.* (7 patients) in Italy (5, 6). We have previously commented on the data for the rate of COVID-19 GBS in the paper of Filosto *et al (7)*. Filosto *et al.* used PCR positive cases attending hospital rather than the seropositivity rates as the denominator for COVID-19 infection in their heavily affected Italian area, and that this would hugely overestimate the rate of GBS associated with COVID-19 (7). Our recalculation of their incidence of GBS in COVID was 10-fold lower than published. Del Castillo *et al.* present an odds ratio (OR) for GBS-COVID versus non-COVID populations based on published statistics of 21.7 (confidence interval (CI) 15.3-30.8) in their Spanish population, and 998 (CI 351-2833) in Filosto *et al*.. In November and December 2020 there were an average of 26100 new symptomatic COVID-19 cases *per day* in the UK alone, and a total of 1.59 million new COVID-19 cases in this period (source https://coronavirus.data.gov.uk/details/cases accessed 11.1.2020). Using del Castillo's point estimates of the OR, between 150 and 4566 extra cases of GBS would have been expected in the UK in the last two months of 2020. Evidently this has not been the case (see figure 1).

Although Vogrig *et al.* describe the studies of Fragiel (21 patients) and Filosto (34 patients) as 'large scale studies', they are too small to make any meaningful epidemiological statement, being very susceptible to small study effects. The problem of 'small study effects' is that they overestimate the positive outcome of any study (8). Although the power of a study depends upon the outcome measures and their standard deviation, often several hundred participants are required to demonstrate a reliable answer, which was not achieved here. Epidemiological series require even greater numbers because of uncontrolled covariables. The 'extensive systematic reviews' of cases described in the letter of Foschi *et al*. further compound the small study effects as almost all of their cases are single case reports. Furthermore, annualised incidence rates extrapolated from short periods of time are susceptible to annual cyclicity as well as the period of the pandemic analysed. To illustrate this point, we display a forest plot of the Incidence rate of COVID-19 GBS using March and April data from the UK to compare to the same period in Spain and Italy. This demonstrates the huge heterogeneity (I^2=98%) in the estimates from these small studies with ours. These studies are so different they should not be meta-analysed or used to generate an incidence summary statistic (Figure 2).

The small geographically regional studies summarised by Vogrig *et al*. may be confounded by the random clustering effect. Pockets of cases described in small case series may be due to random clustering. No disease distributes in perfect correlation to population density alone, and the Poisson

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distribution allows for random clustering unrelated to geographical or temporal influences (9). When significant clusters occur one can investigate for causality. Both the small series of Gigli *et al.* (6) and Tatu *et al*. (10), highlighted by Vogrig *et al*., describe small clusters of GBS with the series of Tatu illustrating a non-COVID-19 GBS cluster in the COVID-19 pandemic (unusually high numbers, none with COVID by any measure). Foschi *et al*. suggested that we look at all the UK records which we now share here. The 2020 UK data from the National IVIG Database are of 939 incident GBS patients. This denominator exceeds the combined Fragiel and Filosto data 17-fold. In our primary paper we explored the geographical correlation of the incidence of COVID-19 around the UK to the incidence of GBS (both of which obeyed the Poisson distribution) but these geographical clusters did not correlate, further indicating the lack of evidence for a significant link of GBS to SarsCov2 infection.

Lastly all our commentators point out, as we did, that looking at linear homologous peptide sequences cannot even begin to explore the complexities of 3-dimensional, non-linear protein, carbohydrate and lipid immunological epitopes already known to be involved in GBS pathogenesis. We would urge caution in making causative linkage from the existing published studies including the excellent study by Lucchese and Flöel (11) {Lucchese letter of correspondence}. Using alternative and arguably better methodology they found “molecular mimicry between the virus and human heat shock proteins 90 and 60, which are associated with Guillain-Barré syndrome and other autoimmune diseases”. The Chiba laboratory from which the putative association with heat shock proteins is drawn published a small, unreplicated study of antibodies to these mitochondrial chaperone proteins (12). Not only are these intracellular antigens, unlikely to be pathogenic targets for serum antibodies, but the described antibodies were found in the CSF only. Furthermore, antibodies to HSP-90 and HSP-60 are found in many autoimmune diseases and are not specific to GBS. Indeed, as Lucchese and Flöel acknowledge themselves, one of the hexapeptides they identified as immunologically relevant (EIPKEE), was deposited on a repository of immune epitopes (Immune Epitope Database, IEDB) based on immunological evidence gathered from a single study of peripheral blood mononuclear cells (PBMCs) of patients with multiple sclerosis (13), which is pathophysiologically very different to GBS. Foschi *et al.* have used a preprint of Butler *et al*. (14) to provide evidence for ‘abnormally high IgG and IgM antibodies to various self-glycans compared to controls’. Butler and colleagues used an exploratory chip array, of unclear quantitative performance, with no corroborative secondary methodology for the positive findings. Only IgG antibodies were found, mostly to non-nerve, and some cases, non-human glycans. Only a minority of cases had an anti-ganglioside antibody that might have been capable of mediating anti-nerve activity. Broad anti-viral immune responses to glycan epitopes displayed by viruses do of course occur, but proving these have neuropathogenic potential goes beyond such findings and should not be used to promote evidence of causative linkage.

The science underpinning the COVID-19 pandemic response in the UK has been heavily criticised in the UK press. It has been more extensive and comprehensive than almost all other countries in the world and our study has built on pre-existing reliable statistical reporting systems. Whilst we cannot, and do not, entirely rule out any link between GBS and COVID-19, it appears to be it appears to be insignificant in population terms in the UK at least, if it exists at all. We appreciate being cautioned to making a definitive statement of ‘no link’ but would also equally strongly caution against the misuse of small, single studies that are likely to reflect significant well-recognised ascertainment and publication bias. In our view, the dangers of over-feeding the medical literature with unsubstantiated claims about an alarming disease are greater than our self-acknowledged cautionary analysis of COVID-19 causality for GBS.

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Figure 1: Daily UK infections with COVID-19 by PCR (blue bars) and monthly cases of GBS (2020 red dotted line: 2019 green dashed line – secondary y-axis) demonstrate no visible increase in GBS in the last quarter of 2020 with a rise in case numbers between 30% and 1000% more than in March/April. Note significant alterations in testing occurred in the UK in April 2020 resulting the subsequent enhanced detection of most symptomatic cases subsequently. Hospital admissions were 30% higher on January 1st 2021 than in April 2020.

*sources: COVID cases (left axis – blue bars) https://coronavirus.data.gov.uk/details/cases : GBS cases (red line) – NHSE National Immunoglobulin Database courtesy MDSAS, Manchester, UK.

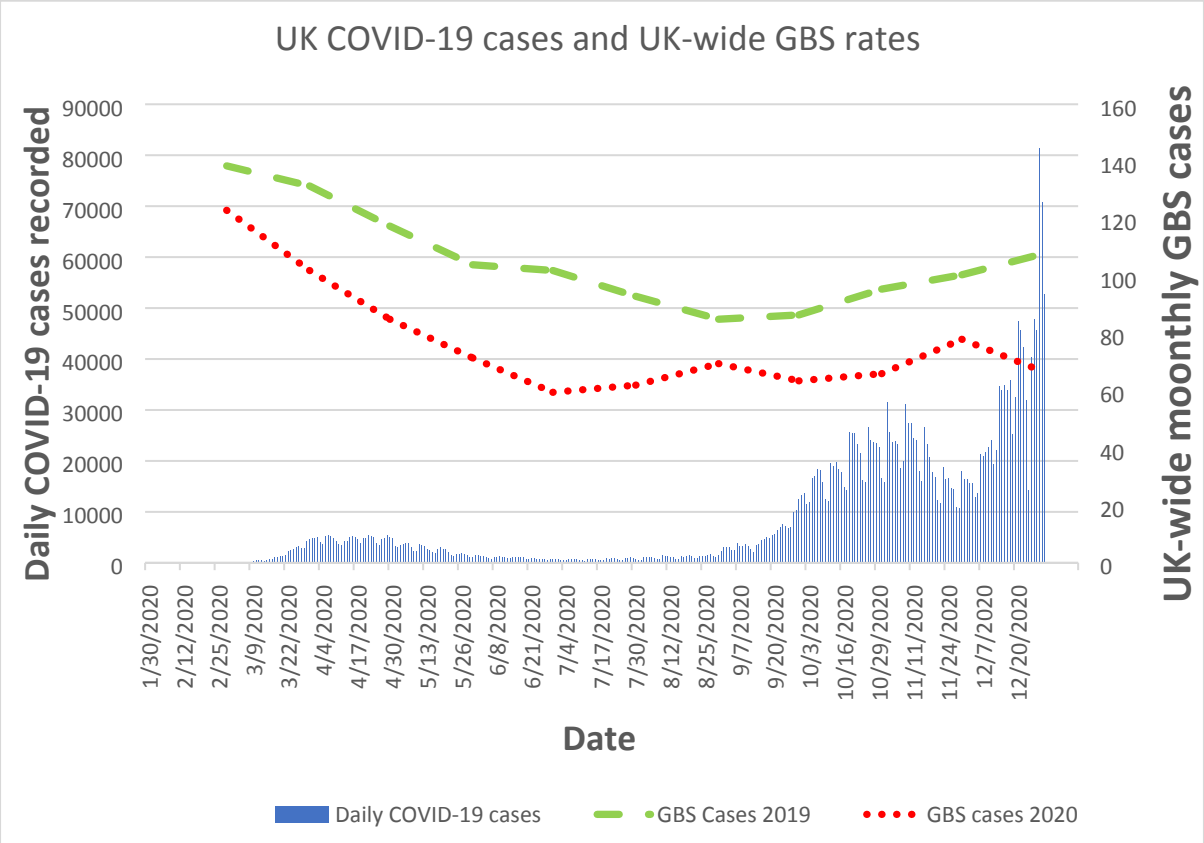
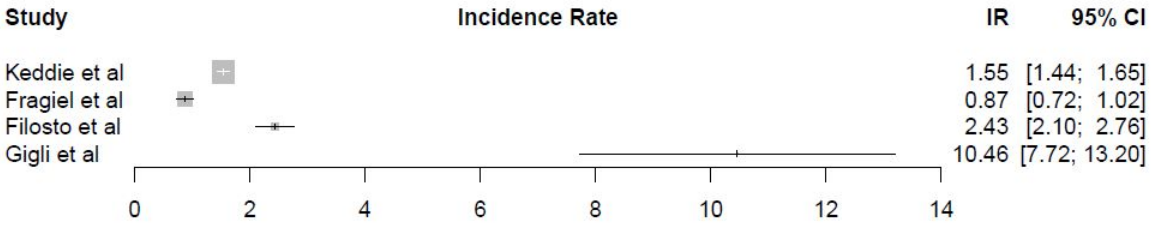


Figure 2: Forest plot of March April Incidence rates per 100000 people per year of GBS from 4 studies (see text). Note the heterogeneity illustrated by I^2=98% indicating that these series cannot be considered in meta-analysis or generate a reliable summary statistic. Box sizes illustrate the relative weight of the estimate displayed.



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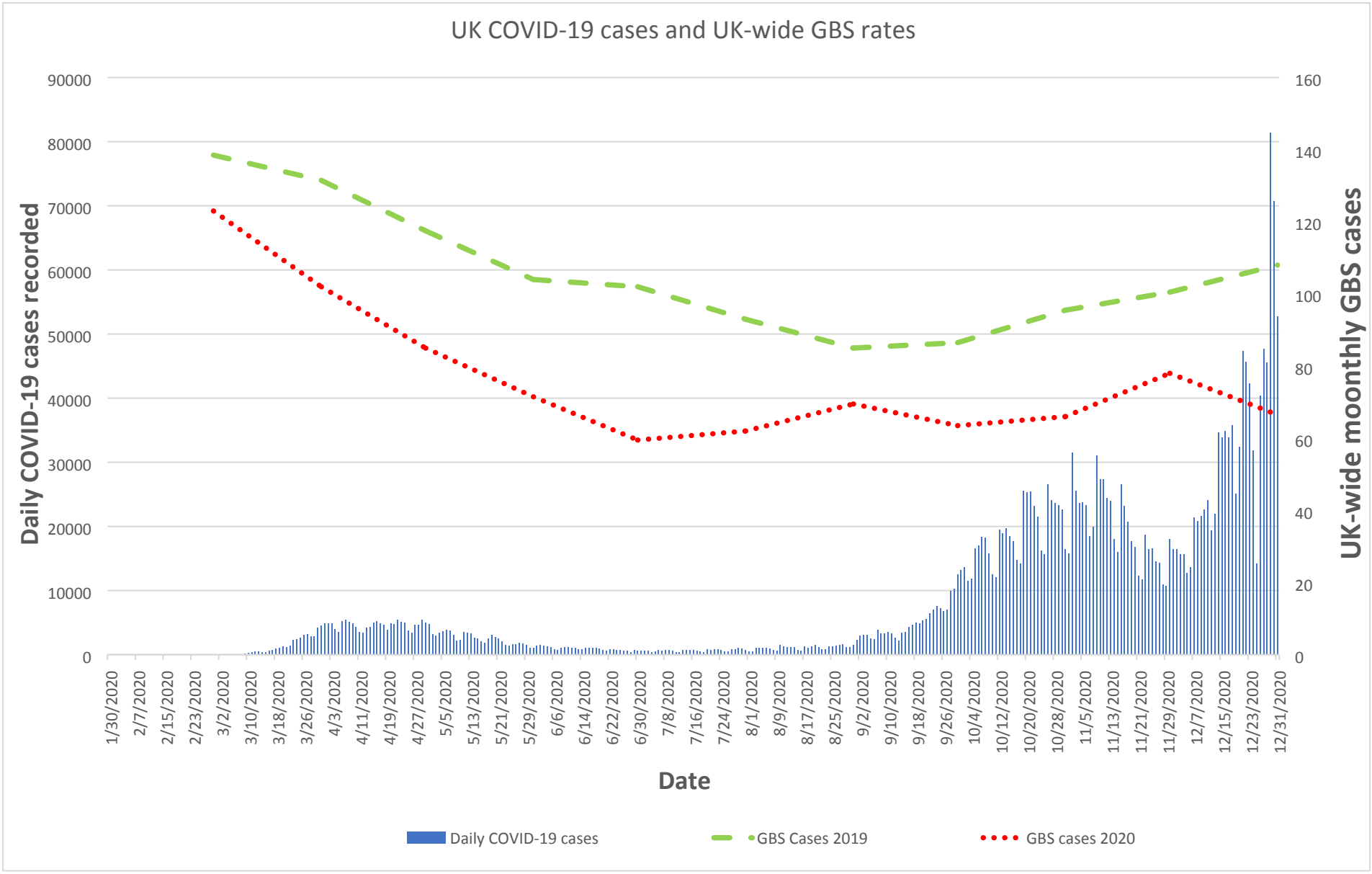
UK COVID-19 cases and UK-wide GBS rates
Daily COVID-19 cases recorded
UK-wide moonthly GBS cases
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
160
140
120
100
80
60
40
20
0
1/30/2020
2/7/2020
2/15/2020
2/23/2020
3/2/2020
3/10/2020
3/18/2020
3/26/2020
4/3/2020
4/11/2020
4/19/2020
4/27/2020
5/5/2020
5/13/2020
5/21/2020
5/29/2020
6/6/2020
6/14/2020
6/22/2020
6/30/2020
7/8/2020
7/16/2020
7/24/2020
8/1/2020
8/9/2020
8/17/2020
8/25/2020
9/2/2020
9/10/2020
9/18/2020
9/26/2020
10/4/2020
10/12/2020
10/20/2020
10/28/2020
11/5/2020
11/13/2020
11/21/2020
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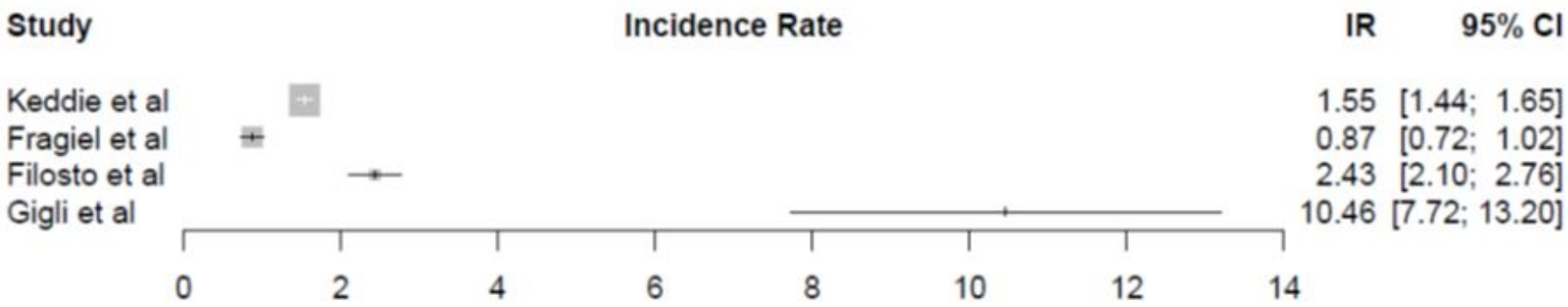
12/7/2020
12/15/2020
12/23/2020
12/31/2020
Date
Daily COVID-19 cases
GBS Cases 2019
GBS cases 2020


Study
Incidence Rate
IR
95% CI
Keddie et al
Fragiel et al
Filosto et al
Gigli et al
1.55 [1.44; 1.65]
0.87 [0.72; 1.02]
2.43 [2.10; 2.76]
10.46 [7.72; 13.20]
0
2
4
6
8
10
12
14

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