COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations.

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Acknowledgements:

MPL is supported by the by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

LQ is funded by Fondo de Investigaciones Sanitarias (FIS), Instituto de Salud Carlos III, Spain and FEDER under grant FIS19/1407 and a personal grant SLT006/17/00131 of the Pla estratègic de recerca i innovació en salut (PERIS), Departament de Salut, Generalitat de Catalunya, and the GBS-CIDP Foundation International.

Ethics:

No ethical considerations to declare

Competing interests statement:

MPL – Consultancy: UCB Pharma Inc., CSL Behring and Polyneuron. PI on trials with Polyneuron and UCB Pharma Inc for which his institution receives investigator fees. DSMB: Octapharma, IoC trial, AstraZeneca Pharmaceuticals

DRC - Consultancy: Amgen Inc., Annexon Biosciences, Argenx SE, Biotest Pharmaceuticals, Inc., Boehringer Ingelheim, Cigna Health Management, Inc., CSL Behring, Grifols S.A., Neuropore, New Enterprise Associates, Inc., Octapharma AG, Passage Bio, Pfizer Inc., Pharnext SAS, Polyneuron Pharmaceuticals, Sanofi-Aventis, Seattle Genetics Inc., UCB Pharma Inc.

Data Safety Monitoring Board: Alnylam Pharmaceuticals, Anavex Life Sciences Corp, PledPharma AB, Momenta Pharma, Hansa Medical AB, Mitsubishi Tanabe Pharma Corporation.

Technology Licensing: AstraZeneca Pharmaceuticals, LP, Genentech Inc., Levicept Inc., Seattle Genetics, Inc., Merrimack Pharmaceuticals, Disarm Therapeutics

RACH has had consultancies with Hansa, Sanofi and UCB.

BJ has no relevant competing interests to declare. BJ has unrestricted financial support for research from Dutch 'Prinses Beatrix Spierfonds', GBS-CIDP Foundation International, CSL-Behring, Grifols, Annexon and Hansa Biopharma. BJ is chair of the Steering Committee of the International GBS Outcomes Study (IGOS).

LQ - LQ has received speaker honoraria from Merck, Sanofi-Genzyme, Roche, Biogen, Grifols, CSL Behring provided expert testimony for Grifols, Johnson and Johnson, Annexon Phaarmaceuticals, Alexion, Sanofi-Genzyme, Novartis and CSL Behring and received research funds from Roche and Grifols

PvD – Grants: Sanquin Blood Supply, Prinses Beatrix Spierfonds, Grifols and Takeda. Expert testimony: Annexion, Argenx, CSL, Octapharma, and Hansa, all outside the submitted work. All grants were paid to the institution research fund.

HW has no competing interests to declare

A worldwide mass vaccination campaign to control the COVID-19 pandemic is imminent. Understanding the epidemiology of rare diseases whose onset will inevitably occur *by coincidence* following SARS-CoV-2 vaccination, but which have little to no evidence of being *caused* by them in any significant number of cases, is critical. Failure to appreciate these issues will result in misattribution of adverse events to the vaccination programme. This could lead to poor uptake of vaccines, delay or even withdrawal of vaccines, or vaccine programmes resulting in unnecessary morbidity and mortality.

Global cases of the COVID-19 respiratory illness caused by the virus SARS-CoV-2 have surpassed 50 million, with a pandemic resulting in medical and economic devastation worldwide. As of late November 2020, four vaccines involving over 100,000 participants have displayed favourable efficacy without significant reported side effects in phase 3 trials. At least 67 COVID-19 vaccines are in phase 1-3 trials: 6 already have limited approval, and 87 are under active animal study investigation (New York Times Vaccine Tracker Nov 18th 2020 - online).

Guillain-Barré syndrome (GBS) is an acute inflammatory peripheral nerve disorder resulting in severe and sometimes lasting paralysis; about one third of patients develop respiratory failure requiring ICU admission and ventilation.(1) GBS is fatal in 3-5% of people, and about two thirds have residual disability. The lifetime individual risk of acquiring GBS is about 1:1,000, and the annual incidence of GBS is approximately 1.7 persons per 100,000 population.(2)(Keddie et al 2020 – in press) Some 1,500 cases of GBS are recorded in the UK each year or by extrapolation about 100,000 worldwide. It is thus an alarming illness for the public and healthcare providers.

Around half of those affected by GBS have a preceding history of an identified infection and two thirds preceding infectious symptoms. The remainder have no overt trigger for their illness. The commonest triggering infection worldwide is gastroenteritis caused by *Campylobacter jejuni*.(3) Many other infections can also trigger GBS including cytomegalovirus, influenza, *Mycoplasma pneumoniae*, the flaviviruses Zika and dengue, and the alphavirus, chikungunya.(4) Notably, during the recent Zika virus epidemic in Latin America, many countries reported a sharp rise in cases of GBS confirmed by strict epidemiological analysis, a relationship widely considered to be causal.(4)

The possibility of SARS-CoV-2 also driving a global spike in GBS has unsurprisingly been eagerly monitored with many cases and small series already published asserting a causal link. However, a surge in GBS cases after the SARS-CoV2 pandemic has not been detected as it happened in the Zikavirus pandemic. In a recent epidemiological study conducted across the UK, there was no increased incidence in GBS during the first wave of COVID-19, and thus no causative link of COVID-19 to GBS can be made, {Keddie et al – BRAIN in press) but a small increase in cases could be hidden behind a much larger decrease in other causes. Filosto et al published a small series of 34 patients from a Northern Italian population of 8.4 million people, reporting a 2.6-fold increase in incidence of GBS, a 3.3-fold decrease in non-COVID associated GBS and a rate of 47.9 cases of GBS per 100000 COVID-19 infections. However, with such small numbers, the confidence intervals of the GBS incidences overlap and using a published Italian Statistical Institute (ISTAT) seroprevalence of COVID-19 for the same period makes the COVID-19 associated rate a maximum of 4.7 cases per 100000 COVID infections. This is not much more than chance. There is currently no definitive evidence that there is an appreciable increase in GBS cases with COVID.

Why does GBS rear its head in the context of the SARS-Cov-2 pandemic and vaccination programmes? To understand this, we need to revisit the 1976/77 USA/New Jersey/76 vaccination programme that brought GBS to world-wide attention. Following dire warnings from experts of pandemic “swine flu”, President Ford instituted a rapid vaccine development program in the USA to prevent this.(5) Unfortunately, the vaccine was found associated with a spike in cases of GBS with an initial calculation of a relative risk of 7.6 (95% CI 6.7-8.6) in the 6 weeks following vaccination, amounting to an attributable risk of just under 1 case of GBS per 100,000 vaccinations.(5, 6) As soon as this was known, the program was halted, but not before implanting the idea of a lasting association between GBS and vaccination.(7, 8) We must not allow hasty and misattributed associations to result from the occurrence of GBS shortly after COVID vaccination without very careful statistical thought and analysis.

Following the “swine flu” programme, numerous national surveillance studies to identify vaccine related GBS have been carried out, notably in the 2008/9 H1N1 influenza seasons, because the H1N1 influenza strain was also of swine origin. Any vaccine related increase in GBS following modern influenza vaccines has been tiny, with the consensus of many robust studies being about 1 additional case per million vaccinations (10-fold less than 1976),(9, 10). In one UK GP database study, influenza vaccination was significantly protective, {Tam et al 2007} as it is in modelling studies of influenza

vaccine where influeza prevalence is >5% and vaccine effectiveness >60%. The risk of hospitalisation after influenza infection is far greater than these at about 17 per million.(11) 22,000 deaths were attributed to influenza infection in the USA in 2019/20.

Multiple other vaccines including hepatitis B, polio, tetanus, meningococcus, rabies an importantly an orally administered adenovirus vaccine have also previously been alleged to be associated with the occurrence of GBS.(12){McNeil MM 2019} No causative links have been conclusively proven despite these individual reports being widely quoted. In a defensive posture, but one which further heightens worries about GBS and vaccines, GBS is recorded as a warning in every vaccination summary of medical product characteristics (SmPC) in the EU or Package Insert (PI) insert in the USA.

All this leads to the relevance of GBS to the current proposed vaccination programme for COVID-19. The world is about to vaccinate at least 1 billion people, and possibly many more if production allows, against COVID-19. The vaccination effort will likely start in December 2020 and continue for several years. It will be the largest mass vaccination campaign ever undertaken. Most COVID-19 vaccinations are based on the Sars-CoV2 spike protein. Sars-CoV2 has not so far been shown to result in a significant increase in GBS. The vaccines developed to this point are delivered by different routes to natural infection and present the S-protein in unconventional ways. However, they contain no additional immunogenic material known or proven to drive GBS. Thus, although an association of any vaccination to GBS cannot be ruled out and we must remain vigilant to its potential occurrence, it is not be presumptively expected.

Herein lie the statistics - within a population of 1 billion people, one would expect about 17000 cases of GBS to occur sporadically per annum, of which 1962 would occur in any 6-week period. When considering a more optimistic 4-billion person immunisation programme conducted over one year, 68000 cases of GBS would be expected to occur naturally within this time period, irrespective of any vaccination programme. Of these GBS cases, 13076 would occur in the 10-week window following double dose vaccination with injections separated by 4 weeks. It is therefore inevitable that many thousands of sporadic cases of GBS caused by other factors will appear temporally associated with COVID-19 vaccination. But, as any statistician can confirm, this cannot be considered causal.

So why is this so important?

Firstly, the rapid vaccine development, accelerated trial programmes, vaccine production and drug licensing that have been necessary to get us to today put pharmaceutical companies and regulators under the microscope of scientific colleagues, the world's press, and every member of the concerned public. Rare diseases with potentially severe consequences such as GBS are thus scrutinised and monitored in minute detail for any increase in incidence. These processes must be transparent and open to outside review. This is already occurring through the regulatory monitoring bodies. Cases of GBS, or other neurological disease, will inevitably occur within the 6-week post-vaccination window by chance alone when such large numbers are vaccinated. Decision makers must not to stop the vaccination programmes unless there is clear evidence of a genuine excess of cases that has been carefully calculated, and even then, only if it is of sufficient magnitude to exceed the benefits of vaccination.

Secondly, rigorous and well-designed GBS surveillance programmes with accurate case definition and ascertainment are needed. Criteria developed by the Brighton Collaboration can be used to verify cases and provide reassurance of diagnostic certainty.(13) These will be critical to accurate case ascertainment. Where practical, ascertainment programmes should be multi-national and include control groups not receiving vaccines. The Peripheral Nerve Society (www.pnsociety.com) and the International GBS Outcome Study group (https://gbsstudies.erasmusmc.nl/) will promote an international effort to prospectively register and collate the numerical incidence of GBS and other relevant autoimmune diseases compared to real time population and vaccination numbers to identify any excess of cases that might lead to real concern about one or more vaccines. These will be critical to determining the risks, if any, of GBS being associated with any of the vaccines. These programmes should also be transparent and open.

Thirdly, governments and medical agencies are about to embark on the most difficult and massive public health intervention in modern history which will have far reaching and long-lasting consequences if we get it right, and more if we get it wrong. Everyone, including scientists, publishers, editors and mass media must thus resist the misuse of statistics and epidemiology that could lead to misattribution of cause, without appreciating the lasting negative consequences for ongoing health and ill health of the world's population.

Responsible citizens understand the value and risk of any vaccine. The individual risk for GBS and other rare complications is likely to be very small indeed, and the benefit of protection against COVID -19 both for individuals and society is far greater. It should be implicit for regulators, pharmaceutical companies, mass media and the general public to understand that rare diseases will inevitably occur by chance during the vaccination window, and that the temporal association between vaccination and GBS onset even in large numbers of individuals within a huge population of billions is not adequate evidence of causation. In those conditions like GBS where minds are pre-programmed to leap to causative assumptions through cognitive bias, this is a particularly vital message to convey.

As part of a larger consortium of neurologists, virologists, vaccinologists, epidemiologists and health-interested agencies that should be immediately convened, we will seek to accurately inform the public, pharmaceutical companies and regulators of this inevitable and important issue.

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