Considerations for causality assessment of neurological and neuropsychiatric complications of SARS-CoV-2 vaccines: from cerebral venous sinus thrombosis to functional neurological disorder

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MB and AT produced the first draft. MB, AT, GW, ME, RT, IG, SP, TS, TP, BM and TN significantly contributed to the first draft. BS contributed additional content post peer review. MB, AT, GW, ME, RT, IG, SP, BS, TS, and TP all reviewed final manuscript. BM and TN provided supervisory input and approved final manuscript.

Competing of Interests

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Introduction

The scientific community rapidly responded to the COVID-19 pandemic by developing novel SARS-CoV-2 vaccines (Table 1*)*. As of early June 2021, an estimated two billion doses have been administered worldwide (1). Neurological adverse events following immunisation (AEFI), such as cerebral venous sinus thrombosis and demyelinating episodes, have been reported. In some cases, these have led to the temporary halting of both vaccine trials and roll-out programmes in some countries. In the absence of clear evidence of causal associations between the vaccine and adverse events, or the rarity of the AEFIs themselves, programmes have thus far been restarted, albeit sometimes with modifications to recommendations (2).

Vaccine	Vaccine type	Developer
Comirnaty (BNT162b2)	mRNA-based	Pfizer
COVID-19 Vaccine AstraZeneca (AZD1222)	Adenovirus	AstraZeneca
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)
Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based	Moderna
Sputnik V (rAd26 and rAd5)	Recombinant adenovirus	Gamaleya Research Institute
Sputnik Light (rAd26)	Recombinant adenovirus	Gamaleya Research Institute
BBIBP-CorV	Inactivated SARS-CoV-2	Sinopharm
CoronaVac	Inactivated SARS-CoV-2	Sinovac
EpiVacCorona	Peptide (spike protein)	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology
Convidicea (Ad5-nCoV)	Recombinant adenovirus	CanSino Biologics
Covaxin	Inactivated SARS-CoV-2	Bharat Biotech
WIBP-CorV	Inactivated SARS-CoV-2	Sinopharm
CoviVac	Inactivated SARS-CoV-2	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products
ZF2001	Adjuvanted protein subunit	Anhui Zhifei Longcom Biopharmaceutical
QazVac (QazCovid-in)	Inactivated SARS-CoV-2	Research Institute for Biological Safety Problems
Inactivated SARS-CoV-2 Vaccine (Vero Cells) [yet unnamed]	Inactivated SARS-CoV-2	Minhai Biotechnology Co.; Kangtai Biological Products

Table 1: SARS-CoV-2 vaccines approved for use by at least one regulatory body at the time of submission (early June 2021) (3).

Transient influenza-like symptoms such as headache, myalgia, and fatigue have been reported in up to 5% of SARS-CoV-2 vaccine recipients in clinical trials (4,5), although these symptoms often indicate an appropriate immune response to vaccination (6). More severe potential adverse effects in the open label phase of vaccine roll-out are being collected through national surveillance systems. In the US, roughly 372 adverse events have been reported per million doses, which is a lower rate than expected from the clinical trials (7).

In the UK, adverse events are reported via the Coronavirus Yellow Card reporting website. As of early June 2021, approximately 250,000 Yellow Cards have been submitted, equating to around 3-7 Yellow

Cards per 1,000 doses (8). For comparison, the 2010 Pandemrix vaccination had a rate of around 0.6 Yellow Card submissions per 1,000 doses (9). Increased pharmacovigilance may lead to surveillance bias (10), safety alerts may lead to notoriety bias (11), and recall bias may also occur. Nevertheless, with large numbers of people being vaccinated, often with a two-dose schedule, rare complications of vaccination may be seen more frequently, and judicious assessment of causality is recommended in each case.

Widespread vaccine take-up is necessary to establish the required herd immunity to stop or slow the pandemic and to prevent the emergence of vaccine-resistant strains (12), as well as to decrease the neurological and neuropsychiatric complications which are associated with COVID-19 itself (13,14). As vaccine uptake is directly influenced by public confidence in the safety of the vaccine, it is critical that those reporting potential neurological and/or psychiatric complications apply stringent methodological approaches to assigning a causal association between the two; as has been undertaken for COVID-19 itself (15).

Here we present a summary of what is currently known about the neurological and neuropsychiatric adverse effects of the currently available COVID-19 vaccines. We review evidence from previous vaccination campaigns and discuss the complexities. Finally, we propose system for AEFI causality assessments.

Neurological adverse events in previous vaccination campaigns

Previous programmes have raised the possibility of adverse neuropsychiatric events to vaccination. Autoimmune encephalitis following influenza and Japanese encephalitis vaccination have been documented (16), as has the likely autoimmune phenomenon of childhood-onset narcolepsy following both influenza H1N1 infection (17) and the associated Pandemrix vaccination (18), which in 2010 was thought to lead to a small increase in narcolepsy rates in several countries (19). As well as the active immunogenic substance, vaccine excipients (e.g. sodium taurodeoxycholate and Thimerosal) as well as the manufacturing process have been potentially implicated in some vaccine reactions, such as febrile convulsions in children administered the inactivated influenza vaccination in 2010 (20). Neurological events attributed to vaccines have also previously led to their cessation from use. A 1976 H1N1 influenza vaccine was withdrawn from use due to a small increase of GBS cases (leading to around an additional one case of GBS for every 100,000 vaccines). (21). Similarly, an intranasal influenza vaccine was also withdrawn in Switzerland in 2001 as it was estimated to have contributed to an extra 13 cases of Bell's palsy per 10,000 vaccinations (22).

It is also recognised that there have been acute neurological responses in previous vaccination campaigns, which although precipitated by the vaccination procedure are not directly related to the vaccine constituents. For example, human papillomavirus vaccination (HPV) vaccinations in Brazil have precipitated functional (non-epileptic) seizures or attacks (a subtype of Functional Neurological Disorder [FND]) (23), which have also been reported following the H1N1 vaccination in Taiwan (24) and South Korea (25). The WHO Global Advisory Committee on Vaccine Safety and Immunisations (GACVS) working group of the World Health Organisation (WHO) recognise such 'immunisation stress related responses' (ISRRs) as a disqualifier in their tool for assessing causality of an adverse event following immunization, which include (but are not limited to) acute stress responses, vasovagal reactions, and dissociative symptoms (26). Many of these ISRRs can be viewed as FND triggered by vaccines. Indeed, FND is commonly precipitated by, and can emerge from, a range of initial 'organic' symptoms which can be due to physical injury or illness. In these cases, vaccination due to the commonly encountered local and systemic reactions is sufficient to precipitate FND (27).

COVID-19 vaccine and neurological manifestations

Clinical trials

At least sixteen SARS-CoV-2 vaccines have been approved for use by at least one national regulatory authority (28) (Table 1), and as of early June 2021, there are around a further 400 vaccines in development, with 102 in the clinical phase (28). Adverse events in the clinical trials - captured using the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Medical Dictionary for Regulatory Activities, under system organ classifications such as central nervous system disorders and psychiatric disorders (29) - indicated limited reports of serious neurological adverse events (4,5). While phase III trials are powered to detect common adverse reactions, association with rare but significant events, such as neurological complications, may not be detected until phase IV or open-label studies. Commonly cited exemplars of this include cases of GBS in association with the 1976/77 US swine influenza vaccination programme (30) and Bell's palsy in association with inactivated intranasal influenza vaccine (22), as discussed above.

Consistent with this, only isolated cases of neurological events were reported in clinical trials of major SARS-CoV-2 vaccines. Three cases of transverse myelitis were reported (2/12,174 in the vaccine group and 1/11,879 in the control arm) in phase III trial of ChAdOx1 vaccine, which led to a temporary halting of the study. Following evaluation, the cases were deemed unlikely to be related to the vaccine and the study continued (31). Medical litigation cases have also been raised, including an anonymous trial

volunteer in India who sued the manufacturers for 'acute encephalopathy' occurring ten days after ChAdOx1 vaccine administration. In this case, the national medical authorities concluded there was no causal link (32).

Few cases of Bell's palsy were reported in the BNT162b2 (Pfizer-BioNTech) trial (4 in the vaccine arm and none in the placebo arm; each arm had >20 000 participants) (4) and the mRNA-1273 (Moderna) trial (3 in the vaccine arm and one in the placebo arm; each arm had >15 000 participants) (5). Despite uneven distribution in the vaccine versus placebo arms, such numbers were in keeping with the expected rates based on the baseline prevalence of Bell's palsy (20-40/100,000 annually) (33). Aside from this, the BNT162b2 and mRNA-1237 trials reported no other notable patterns between treatment groups for other neurological or neuroinflammatory events (4,5).

Numerical imbalances were also reported for some adverse neurological events in the phase III study of the Ad26.COV2.S (Johnson & Johnson/Janssen) of over 43,000 individuals (of whom >21,000 received the vaccine) (34). In the vaccination group, there were four events of seizures (versus one in placebo group) and six events of tinnitus (versus 0). One case of GBS was also seen in the vaccine arm. There were also eleven thromboembolic events in the vaccine arm (compared with three in the placebo group), including one case of cerebral venous sinus thrombosis with cerebral haemorrhage. This case was associated with thrombocytopenia, disseminated intravascular coagulation, and later was also found to have developed antibodies to platelet factor 4. The trail was paused and subsequently restarted following an external review as causality could not be determined at the time (35). Causality has not been confirmed for other events, as underlying medical conditions may have predisposed the affected individuals. Detailed post-approval surveillance of these events was advised (34).

The phase III trial of the Sputnik vaccine did not feature any significant neurological adverse events in over 16,000 participants in the vaccine group (36). Full peer-review publications of some other vaccine phase III trials, with an estimate of neurological adverse events, are currently awaited.

Post-approval surveillance

That rare, but significant, adverse events may only be detected following large-scale, open-label monitoring is exemplified by the emergence of vaccine-induced thrombosis with thrombocytopenia (VITT). VITT resembles heparin-induced autoimmune thrombocytopenia, manifesting with low platelet count and extensive thromboses. VITT has been reported to arise due to the development of antibodies to platelet factor 4, typically four to twenty-eight days after the first dose of an adenovirus-

vector-based vaccine (37). The most common neurological manifestation of VITT is cerebral venous sinus thrombosis (CVST), but arterial stroke is also a recognised complication (38).

Concerns about the association of VITT with SARS-CoV-2 vaccination were first raised in March 2021 (39), and cases reported in the literature followed shortly afterwards (40,41). The unique clinical features of the syndrome and the consistent temporal relationship with the vaccine led to the confirmation of its causative role. In response to this, many countries, including Germany, US, Norway, Canada, the UK and others, suspended or amended the target age ranges of the implicated vaccines: ChAdOx1 and Ad26.CoV2.S (42,43). As of 2nd of June 2021, there have been 372 cases of VITT reported to the UK Medicines and Healthcare products Regulatory Agency (MHRA), of which 135 had CVST (8). This translates to an overall incidence of 14.2 cases per every million doses administered. An epidemiological study of Danish and Norwegian adults reported a higher incidence of CVST post ChAdOx1 vaccine with an excess of 2.5 events for every 100,000 vaccines administered (44).

Neurological adverse events are tracked by national regulatory bodies worldwide. This includes the UK MHRA's Yellow Card system as well as the US Centers for Disease Control and Prevention's Vaccine Adverse Event Reporting System. Both agencies run rapid cycle analysis as well as comparison of observed versus expected rates to allow early safety signal detection. Several hundred Yellow Card reports for Bell's palsy, seizures, GBS and transverse myelitis have been submitted following almost 65 million doses of COVID-19 vaccinations administered in the UK (8). So far, these numbers do not exceed the natural expected case rates, although reports continue to be closely monitored. Similarly, there are only individual case reports of neurological adverse events following COVID-19 vaccines in the literature; these include GBS (45), Bell's palsy (46), acute disseminated encephalomyelitis (ADEM) (47), transverse myelitis (48), delirium (49), and seizures (50). The authors of these articles warn against attributing causality based solely on the temporal association.

Several videos of neurological and neuropsychiatric post-vaccination symptoms and signs have been shared on social media, many of which have been widely shared and in some cases picked up by news channels (51). In some of these widely circulated videos, from countries such as the United States, objective clinical features suggestive of functional neurological disorders (FND) have been identified, although clinical evaluation would be required to confirm this (52). Further, 64 anxiety-related adverse events (such as syncope, sweating or dizziness) were reported in clusters following Ad26.CoV2.S vaccination in the US (53). All were classified as non-serious, but the authors highlighted that the importance of recognising such events to provide reassurance to the affected individuals and to other members of public attending vaccination centres.

Considerations for causality assessments

There are several tools for assessing causality for post-vaccination sequelae, including the WHO's GACVS causality assessment tool (26). In Table 2 we correlate the GACVS criteria with the well-known Bradford Hill criteria for causality (15), and discuss the implications for establishing causality in neurological adverse events associated with COVID-19 vaccination, including FND.

<u>Assessing causality</u>

Before proceeding to any causality assessment, the adverse event diagnosis must be first validated. This can be done using the Brighton Collaboration guidance, which provides definitions and levels of diagnostic certainty for neurological conditions such as GBS and Miller-Fisher syndrome, transverse myelitis, Bell's palsy, encephalitis and ADEM as well as generalised convulsive seizures (54). Nevertheless, there are two principal limitations to using well-established case definitions. First, some recognised, but atypical variants will not meet the diagnostic criteria, precluding causality assessment (an example of this is facial diplegia with paraesthesia variant of GBS) (55). In these cases, clinicians may agree on working definitions for such condition to include them in the surveillance sensitivity analysis (56). Second, no case definitions are available for new and emergent adverse events, such as VITT. In the case of VITT, the consistent clinical presentation, specific laboratory features (such as thrombocytopenia and positive platelet factor 4 antibodies), as well as the objective radiological findings allowed the scientific community to rapidly establish diagnostic criteria (38,41). Case definitions are being refined in larger cohort studies to reflect clinical variants not meeting the original definitions (for example, up to 5% of patients with VITT may have normal platelet count at presentation) (57). Establishing case definitions is, however, is a particular challenge for adverse events with variable presentations and without specific diagnostic tests, such as FND.

Once the clinical case definition is ascertained, one can proceed to the causality assessment. Using questions summarised in Table 2, the WHO algorithm for AEFI groups events into five categories: consistent with causal association, indeterminate, inconsistent with causal association, unclassifiable (insufficient information) or unsuitable for causality assessment (not meeting clinical case definitions). Events are classified as inconsistent with causal association if there is a strong suspicion of alternative causes and as consistent with causal association if there is no alternative aetiology and previous evidence suggests association the vaccination (26). A consequence of this is that for any new vaccine, all adverse events will be initially classified as 'indeterminate', until further evidence becomes available. This significantly limits the use of these criteria for assessment of adverse events following novel vaccines, such as large-scale programmes for SARS-CoV2.

Instead, we propose classifying cases as: probable, possible, and unlikely, considering the temporal relationship, individual risk factors and the likelihood of an alternative aetiology (Table 3). This approach may support clinicians in assessing individual patients where the evidence from the literature is sparse, but it should not replace the statutory reporting to regulatory bodies.

WHO GACVS Criteria	Bradford Hill equivalent	Considerations for assessing causality of covid-19 vaccination in organic neurological adverse events	Considerations for assessing causality of SARS-CoV-2 vaccination in functional neurological disorders
Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	Consistency, strength & experimental evidence	Limited evidence exists for new products, such as SARS-CoV-2 vaccines. Isolated cases, such as CVST with thrombocytopenia in phase III Ad26.COV2.S trial, might have been reported in the clinical trials. Currently, multiple case reports and some epidemiological studies link VITT with adenovirus-vector vaccines. On the other hand, only isolated case reports are available for Bell's palsy, GBS, transverse myelitis and seizures, with no evidence from epidemiological studies.	In some widely circulated videos of SARS-CoV-2 vaccine reactions, objective clinical features suggestive of FND have been identified (52,58). Case reports of probable FND precipitated by SARS-CoV-2 vaccines have been recently published (59).
Is there a biological plausibility that this vaccine could cause such an event?	Biological plausibility	The immune response to SARS-CoV-2 vaccines is the most likely mechanism for neurological AE. For example, vaccines are a recognised risk factor for GBS. However, confirming exact mechanisms, and identifying responsible components of the vaccine (if any) may take a long time even in well-defined AE such as VITT.	Physiological reactions (e.g. vasovagal symptoms or flu-like symptoms), as well as injection site pain, may trigger and/or evolve into functional symptoms (27).
In this patient, did a specific test demonstrate the causal role of the vaccine?	Coherence	Antibodies to platelet factor 4 have been used to confirm the diagnosis of VITT. However, it is recognised that not all patients will uniformly test positive. For other neurological events, specific tests can demonstrate the diagnosis (such as nerve conduction studies in GBS) but will not be able to attribute it directly to the vaccine.	FND is identified by positive clinical features. FND does not implicate specific vaccine constituents - it is precipitated by the physical procedure of being vaccinated.
Did the event occur within a plausible time window after vaccine administration?	Temporality	Most immune-mediated events are expected to develop days to weeks after vaccination. For VITT, the timeline is 5 to 30 days, although patients may present later (as thrombosis may be initially asymptomatic). For other immune-mediated neurological conditions, such as GBS or transverse	FND precipitated by vaccination can potentially arise within minutes if precipitated by the vaccination procedure itself but could also develop over days if precipitated by physiological effects of vaccination e.g., vasovagal or 'flu-like side effects.

		myelitis, the standard cut-off is 42 days, although additional sensitivity analyses are often run using longer time intervals (up to 3 months). Events developing <24h (except for seizures) would be unlikely to be attributed to the vaccination. (21,60).	
Could the current event have occurred in this patient without vaccination (background rate)?	Specificity	VITT has not been described prior to the adenovirus-vaccines and so baseline rates of CVST with thrombocytopenia are unknown. Epidemiological studies may use CVST only as baseline rate, but such approach is limited. Baseline rates for GBS, transverse myelitis and Bell's palsy are routinely used in vaccine surveillance. Beyond spontaneous occurrence, one must consider explaining the event by risks factors and alternative aetiologies. For example, one's risk of Bell's palsy is increased in pregnancy, whereas GBS may be triggered by infective illness.	FND is common (27) and in many cases would arise independently of vaccination, although, as discussed above, it may be a precipitating factor in some cases. Sociological and pandemic factors may further predispose those with a risk of FND to develop the disorder from a precipitating stressor, such as vaccination (61).
Have similar events been observed in previous vaccination campaigns?	Analogy	Examples of neurological events associated with vaccinations include: 1976 Swine 'Flu vaccination association with GBS (21,62). 2001 intranasal 'flu vaccine association with Bell's palsy (22). 2010 childhood-onset narcolepsy following Pandemrix vaccination (17).	Functional symptoms have been described following HPV (23,63) as well as the H1N1 vaccination (24,25) campaigns.

Table 2: *Criteria for defining causality in vaccine related adverse events adapted from WHO criteria* (56) *and from Bradford Hill criteria* (64).

Causality Label	Assessment Criteria	Considerations for Neurological AEFI
Probable	Typical time frame. AND No indication of an alternative aetiology. AND No risk factors.	For immune-associated AEFI, <6 weeks from vaccination. No risk factors or alternative aetiology identified by the means of clinical, laboratory, radiological and electrophysiological assessment, as indicated.
Possible	Plausible time frame, but outside of typical. AND/OR There may be an indication of an alternative aetiology and/or risk factors, but these are unlikely to explain the event.	For immune- associated AEFI, 6-12 weeks from vaccination. Presence of risk factors, such as a previous episode of Bell's palsy in a patient with post-vaccination Bell's palsy.

| Unlikely | Timeline not in keeping with prior established temporal associations AND/OR Alternative aetiology and/or risk factors fully explain the event. | For immune- associated AEFI, <24 hours or more >12 weeks from vaccination. Clear alternative aetiology, such as Campylobacter diarrhoea preceding GBS. |

Table 3: *Suggested criteria for labelling causality in neurological AEFI.*

High-quality randomised controlled trials may often be one of the strongest means by which to assess causality in AEFIs, however in situations such as the ongoing SARS-CoV-2 vaccination campaign undertaking such trials post-licencing may not be feasible, or ethical (65). Instead, alternative methods of establishing causality, such as triangulation, may be used. Triangulation, a process akin to the Bradford Hill criterion of consistency, involves the integration of results from different epidemiological methods (e.g., RCT and observational cohort studies) with different inherent biases. If two or more methods point towards a potentially causal event (particularly if the association is maintained amongst differing populations), this strengthens conviction in causal association (66). As well as this, although a mechanism (the Bradford Hill criterion of 'biological plausibility') is often preferred in causality assessments, it may not be immediately apparent, and causality should not be refuted simply on the absence of biological mechanisms, particularly should the other evidence for causality be strong.

Although associations between SARS-CoV-2 vaccines and neurological adverse events may arise, these tools reiterate that caution must be exercised before causality is determined. Alternative aetiologies or recurrence of previous neurological disease may be responsible for the observed events, as was the case in some of the neurological AE associated with the ChAdOx1vaccine (31). Further, the baseline rate of a condition may account for its occurrence in vaccinated population (67).

Additional attributes related to the current SARS-CoV-2 vaccination programmes which may need to be considered when assessing causality include (but are not limited to) a) the two-dose nature of some vaccine programmes, b) the possibility of some patients, e.g. due to vaccination supply changes, receiving two separate brands of vaccine in a single dose schedule c) the individual's prior exposure to SARS-CoV-2 (i.e. antigen formation and/or development of neurological complications of COVID-19 itself). These factors will also remain important if in future a seasonal SARS-CoV-2 'booster' vaccination is required.

Practical considerations

While causality is under intense study, a practical issue for clinicians is advising on SARS-CoV-2 vaccine uptake in patients with a history of disabling or life-threatening GBS, acute disseminated encephalomyelitis or transverse myelitis, which are thought to have been linked to previous

vaccination. Bayesian inference may suggest updating the probability of neurological complication based on an individual's prior history. However, as there are no confirmed signals that these conditions occur with SARS-CoV-2 vaccines, cautious advice must be given. Other factors which may help shared decision-making include the population prevalence of COVID-19, the individual's risk of mortality from COVID-19 and patient preference.

In the current rapid worldwide vaccination campaign, healthcare regulatory authorities have tended to either halt vaccination campaigns or recommend their use only in those with risk factors for COVID-19 in response to potential adverse events (39,42,43). The latter appears to be a sensible course of action whilst causality is swiftly reviewed, given the high rates of known complications of COVID-19 itself.

<u>Legal issues</u>

The potential for neurological AEFIs (including FND) to SARS-CoV-2 vaccines raises important medico-legal questions. An effective and fair compensation scheme for AEFIs is integral to maintaining public trust in vaccination campaigns (68). In the United Kingdom, for example, vaccine recipients (including of a SARS-CoV-2 vaccine) are entitled to claim compensation for 'severe disability' resulting from a vaccination (69). Other methods of seeking compensation, including indemnification in clinical trials of vaccines and direct legal action against vaccine manufacturers, may also be applicable in the SARS-CoV-2 vaccination campaign. We are not aware of any precedent in this area regarding severe and disabling FND resulting from vaccination, but the fact that the vaccine constituents are not implicated, and significant or full recovery always remains possible, complicates an already complex field, in which 65% of historical claimants to the UK scheme have been unable to definitively prove causality (68).

Functional Neurological Disorder (FND) reactions to vaccination

As we have seen, an expected response to the vaccination programme, particularly in younger people, may be acute FND. Patients with FND may present with a range of neurological symptoms including, but not limited to, seizures, sensory abnormalities, gait or balance disturbance, and weakness. Symptoms arise as a disorder of neurological function as opposed to structural lesions, and often mimic patients' expectations of illness models rather than symptoms seen in organic neurological disorders. These factors can lead to misinterpretations of such symptoms as being under the patient's control and fuel both stigma and rejection of the diagnosis (27). As well as this, healthcare workers are often unaware of, or lack confidence eliciting, the 'positive' clinical features that can reliably distinguish it from other neurological disorders (27).

Our understanding of FND has developed dramatically in the last decade, and current models of the disorder challenge stress or psychological processes as the sole aetiological factor. Stress is not always present or relevant, and its primacy in older 'psychogenic' or 'conversion' models of FND has been replaced by more nuanced biopsychosocial models that, whilst acknowledging the important role of stress, do not assume its relevance for all. These models focus on cognitive and neurobiological processes underpinning symptom formation and persistence. Alongside the reduced primacy of psychological factors has been the acknowledgement of the importance of positive neurological signs such as Hoover's sign, which has a specificity of at least 95% in functional leg weakness (27). It is recognised that a compassionate, thorough and open explanation of the disorder improves understanding and acceptance of the diagnosis and is a critical first step to successful treatment (27).

In many cases, FND is precipitated by physical disorders, sometimes relatively 'minor' injuries or accidents. In the case of vaccination, it is plausible that physiological reactions (e.g., vasovagal symptoms or influenza-like symptoms), as well as unilateral pain from the injection site, may trigger and/or evolve into functional symptoms (61). Indeed, FND has been reported in response to previous vaccination campaigns, and case reports of FND precipitated by SARS-CoV-2 vaccination have been published (59). Despite this, clinicians must continue to be just as judicious in attributing causality of SARS-CoV-2 vaccines to FNDs as with any other neurological adverse event.

The capacity for functional symptoms to develop in response to vaccination may be increased due to wider factors of the global SARS-CoV-2 vaccination campaign. Patients with FND have been shown to have heightened suggestibility (70), which is currently understood in a Bayesian framework to reflect a tendency to form over-precise 'priors' (71). Attentional focus on potential neurological side effects, particularly in the context of extensive media interest, may result in somatic hypervigilance for specific symptoms in some individuals, which in turn is likely to contribute to an increased risk of FND (52). Conceptually, this is supported by the improvement of cases of FND in response to previous vaccination campaigns once media coverage of the events ceased (72). Furthermore, the capacity of social media to facilitate the dissemination of information, as well as mis- and disinformation, may contribute to the worldwide spread of functional reactions to vaccines (72).

The influence of media coverage and public perception of vaccine reactions on susceptibility to FND offers a potential opportunity for healthcare professionals to reduce the incidence of expected vaccine related FND. The better informed potential vaccine recipients and the wider public are about the potential for FND in response to SARS-CoV-2 vaccines, the better the outcomes are likely to be for those who develop FND in response to vaccination (58). Additionally, clinicians and wider health authorities are implored to strike a balance between thorough investigation and reassurance in

patients in whom a functional reaction is identified. This is likely to prove challenging in some situations, particularly given the role of social media, however sensitive and informed handling of situations is likely to lead to better outcomes for patients and the wider vaccination campaign.

Occasionally, functional symptoms can 'spread' between individuals as 'mass psychogenic (functional) illnesses' after vaccination. These clusters of functional illnesses occur most often within cohesive social groups such as schools or workplaces and can arise in many settings in response to stimuli which are perceived as noxious. There were cases of functional disorders following the H1N1 vaccination in Taiwan (24) and South Korea (25). In both countries, these predominantly affected schoolchildren, and in some cases in Taiwan, symptoms of functional dizziness and weakness spread in clusters, all of which resolved without medical intervention. This phenomenon has been echoed in multiple other countries and in response to different vaccines (73). In situations in which functional illnesses have arisen contemporaneously with vaccination programmes, misunderstanding of causality and association has led to significant increases in vaccine hesitancy; in Colombia, following a large-scale outbreak of functional symptoms, HPV vaccine course uptake decreased from 88% to just 5% (63).

Inappropriate recognition and management of FND may be disruptive to vaccination programs. To this end, vaccine providers should have training on recognising functional disorders which should be clearly distinguished from other AEs, such as allergic reactions to the vaccine. Although symptoms of FND are disabling and in some cases can be chronic, patients can be reassured that FND does not equate to any structural damage to the CNS. In the absence of this clarity, vaccine-associated FND has the capacity to contribute significantly to vaccine hesitancy (74).

Conclusion

Neurological and neuropsychiatric adverse events have been reported in clinical trials of various SARS-CoV-2 vaccines and, more often, in open-label monitoring. In many cases, no definitive evidence has yet supported causality. Despite this, there are recognised rare adverse events which have been causally linked to SARS-CoV-2 vaccines, for example VITT. The necessary ongoing surveillance work is in progress, however the current advice that the benefit of the vaccination outweighs the risk appears to be accurate from a neurological standpoint. Heightened reporting of adverse events, for example via the Yellow Card system, may be in part due to increased pharmacovigilance.

In order to establish causality clinical case definitions must be established, for example via the Brighton collaboration guidelines for conditions recognised to be associated with vaccination, and pro-active clinician-led definitions in emergent conditions (such as VITT). In assessing causality, tools such as the WHO GACVS or Bradford Hill criteria may be used, however we additionally propose criteria

which classify associated neurological or neuropsychiatric events into probable, possible, and unlikely cases, considering the temporal relationship, individual risk factors and the likelihood of an alternative aetiology. In such cases as the urgent SARS-CoV-2 vaccination campaign in which ongoing RCTs may be unfeasible and/or unethical, epidemiological methods of causality assessment such as triangulation may be used.

Regardless of current surveillance of neurological adverse events, it is increasingly likely that a significant minority of vaccine recipients will develop both organic and/or functional reactions to vaccine administration, which have already been noted in previous vaccination campaigns, as well as on videos and in case series during the COVID-19 pandemic. FND reactions are real and distressing, although require different management strategies, and lack of public understanding of FND reactions to vaccination may significantly increase the risk of vaccine hesitancy. Particular features of the SARS-CoV-2 vaccination campaign, including the role of social media in spreading (mis)information on vaccination side-effects, as well as intense media interest, may mean individuals are further predisposed to FND reactions. Despite this, these avenues also offer clinicians opportunity to better inform potential vaccine recipients, and in doing so potentially reduce the incidence of acute FND reactions.

It is important that those working in the clinical neurosciences are abreast of the evidence for and against potential associations, including background rates and the potential for FND manifestations to both care for our patients and to not hamper ongoing vaccination efforts. At the individual level, clinicians are encouraged to have collaborative discussions with patients on the potential for neurological and neuropsychiatric complications of SARS-CoV-2 vaccinations.

Conflicts of interest

The authors declare no conflicts of interest.

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