Letters

Should we now discuss possible COVID-19 vaccine negative effectiveness?

Commendations are due to *AJGP* and Professor Robert Tindle for their recent article published in the April 2024 issue, including the bold statement: 'Because COVID-19 vaccines were approved without long-term safety data and might cause immune dysfunction, it is perhaps premature to assume that past SARS-CoV-2 infection is the sole common factor in long COVID'.[1] The possibility that long COVID could be related to the vaccines is important, but the focus here is on the notion that the vaccines could cause some sort of immunosuppression, especially, as noted by Professor Tindle, since the spike protein 'exhibits pathogenic characteristics' – to say nothing of the 'class switch to IgG4 antibodies', which Professor Tindle thinks could lead to autoimmunity and cancer. I have speculated as much, noticing many data sets indicating that not only does COVID-19 vaccine effectiveness appear to decline very rapidly (varyingly for infections, hospitalisations and even deaths), it can reach zero (no effectiveness), and beyond (negative effectiveness).

For example, a recent *The Lancet Regional Health* paper states: 'Compared to a waned third dose, fourth dose VE [vaccine effectiveness] was 13.1% (95% CI 0.9 to 23.8) overall; 24.0% (95% CI 8.5 to 36.8) in the first two months post-vaccination, reducing to 10.3% (95% CI –11.4 to 27.8) and 1.7% (95% CI –17.0 to 17.4) at two to four and four to six months, respectively'.[2] Given the wide confidence intervals, these latter figures could be negative. A study by Shrestha et al found each vaccine dose was associated with a higher number of infections, with those on zero doses faring best.[3] A study published in the *New England Journal of Medicine* found vaccine effectiveness dropping dramatically, including for severe COVID, with the previously infected and unvaccinated having lower infection rates than the never-infected double dosed.[4] And a British study revealed the effectiveness of one to two doses of AstraZeneca and Pfizer vaccines dropping to zero, and turning negative, after only two to three months.[5] There is much more in the literature; word count prevents me from listing all such evidence.

Relatively few articles dare to explicitly discuss the phenomenon of perceived COVID-19 vaccine negative effectiveness, though Monge et al at least acknowledged it and tried to explain it away with a hypothesis around some selection bias.[6] A *British Medical Journal (BMJ)* rapid response listed some of the evidence for this disturbing phenomenon, and called for further research.[7] Furthermore, an unofficial 'series' of four articles, involving Peter Doshi, in the *Journal of Evaluation in Clinical Practice*, the last of which was published this year, indicates that issues with counting windows have likely led to exaggerations of COVID-19 vaccine effectiveness and safety estimates, for both the clinical trials and later observational studies.[8] Finally, in contrast to Monge et al, a new Czech study by Fürst et al found strong evidence for the healthy vaccinee effect;[9] this also seems to be evident in the recent and much-publicised Australian study promoting booster shots, which revealed an uncharacteristically high unvaccinated rate in elderly Australian aged care residents.[10]

All this makes it plausible that the COVID-19 vaccines have always had an effectiveness that was very low, zero, or even negative, with inadequate methods allowing for a highly exaggerated effectiveness initially – an exaggeration that is lessened with time. It is, as Professor Tindle noted, possible that the vaccines could be causing immunosuppression. With the ubiquitousness of the vaccines, and the fact that some vaccine mandates are still in place, to say nothing of the upcoming Senate inquiry into excess mortality,[11] I suggest we investigate this further.

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WE READ WITH INTEREST Professor Robert Tindle's recent Viewpoint article published in the *AJGP* April 2024 issue that rightly draws attention to the plight of long COVID sufferers, and the need to better understand the condition's aetiology, clinical course, management and to tailor care.[1] However, we write to provide evidence to counter the unsubstantiated assertions that COVID-19 vaccination is causally associated with long COVID.

COVID-19 vaccination has saved millions of lives and reduced morbidity and mortality from SARS-CoV-2 worldwide, including in Australia.[2–4] Additionally, COVID-19 vaccine boosters continue to provide protection against serious disease and death, particularly in people at highest risk such as the elderly.[5,6] Like any vaccine, there are expected and common self-resolving side effects, such as muscle aches, fatigue and fever in some recipients; such events have been extremely well studied in the largest body of clinical trials ever seen and continue to be closely monitored using active surveillance in Australia.[7]

Importantly, to understand whether vaccines cause any adverse event, detailed epidemiological studies of association, as well as biological plausibility, are needed. To date, extensive studies of a range of potential adverse events have shown only a few very rare types of events are linked to COVID-19 vaccines. These include myocarditis following mRNA vaccines, pericarditis following mRNA and adjuvanted protein subunit vaccines, and vaccine-induced thrombosis thrombocytopenia syndrome following viral vector vaccines that are no longer used in Australia.[8–10] Multicountry studies, involving hundreds of thousands of people, continue to be conducted to examine a range of health outcomes.[11]

Professor Tindle's discussion failed to cite the extensive body of evidence demonstrating that vaccination protects against long COVID. This includes at least four systematic reviews of more than 40 individual studies.[12–15] Further, more recently published studies[16–19] using primary care electronic health records to ascertain long COVID diagnoses were conducted across five countries (UK, Spain, Norway, Estonia, USA) during circulation of SARS-CoV-2 pre-Omicron and Omicron variants. These studies included more than 25 million adults and over one million children. Collectively, the systematic reviews and other high-quality publications indicate that COVID-19 vaccination reduces the risk of long COVID and post-COVID-19 conditions by approximately 30–50%. Protection is evident for both primary vaccination and boosters. Although the precise mechanism by which SARS-CoV-2 infection leads to long COVID is not known and the condition is likely multifactorial, the prevention of post-COVID-19 conditions by vaccination might occur through either or both of prevention of infection and mitigating the impact and severity of breakthrough infection.

Alongside Professor Tindle, we fully support the need for further high-quality data collection and research into long COVID, as recommended by the Australian Parliamentary Inquiry.[20] We also appreciate the importance of conducting and transparently sharing surveillance and vaccine safety data; however, we emphasise that great responsibility is needed for all healthcare professionals to draw on the most robust scientific evidence available.

General practitioners (GPs) and practice nurses are critical partners in vaccination, distilling complex information into guidance for their patients on the benefits and risks of specific vaccines during shared decision making. With misinformation and vaccine hesitancy increasing globally and locally,[21] we suggest that trusted clinical guidelines developed by expert groups, such as those contained in the Australian Immunisation Handbook, are relied upon by GPs in their quality practice.[22]

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I AM GRATEFUL for the valuable insights shared by Professor Robert Tindle in his article 'Long COVID: Sufferers can take heart', published in the *AJGP* April 2024 issue.[1] Of most importance is the understanding of the pathogenic nature of the COVID-19 spike protein – found both in the COVID-19 vaccines and the COVID-19 virus. This view is also supported by other Australian academics and has been termed 'spikeopathy'.[2]

Professor Tindle's concerns about 'Long Vax(x)' very much echo conditions I have observed working as a general practitioner. I have seen patients present with long COVID symptoms post COVID-19 vaccine without prior COVID-19 infection. I have also observed patients with long COVID that has been acquired post COVID-19 infection, who have experienced a worsening of their symptoms post COVID-19 vaccination. This is consistent with studies that have shown a worsening of symptoms in 21%[3] to 31%[4] of long COVID sufferers post COVID-19 vaccination. Although the remainder of patients in these trials experience either improvement or no change in their long COVID symptoms, it leaves the patient in a Russian roulette-type scenario when they are already barely functioning.

Although Professor Tindle lauded the availability of antivirals, more recently, access to antiviral treatments was tightened.[5] Access to early antiviral therapy might help prevent long COVID cases and assist long COVID sufferers' worsening in the setting of repeat infections; however, the Pharmaceutical Benefit Scheme (PBS) criteria do not include this vulnerable group. Many long COVID sufferers struggle to work and cannot afford the $1000 non-PBS fee.

I have personally suffered from a COVID-19 vaccine injury leading to dysautonomia, small fibre neuropathy, thyroiditis and mast cell activation syndrome (MCAS). Subsequent COVID-19 infections worsened these conditions and contributed to Epstein–Barr Virus (EBV) reactivation. These personal challenges have given me insights I would not have otherwise had into the numerous immunological effects of the manufactured vaccine spike protein.

I do take heart in the growing awareness of the complications of COVID-19 infection and vaccination, and the role that spike protein plays in both. Understanding of 'spikeopathy' will assist with safer vaccines and more effective treatments for long COVID and vaccine injuries.

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Reply

My viewpoint article, published in the *AJGP* April 2024 issue,[1] addresses aspects of long COVID involving medical practitioners, health administrators, support systems and sufferers. I thank the three correspondents, (hereafter designated as Drs Lataster, Liu et al and Murnane), for their insightful comments.

Vaccine efficacy

The correspondents address the efficacy of COVID-19 vaccines for primary SARS-CoV-2 infection and disease, long COVID and putative vaccine adverse effects.

The fact that Drs Lataster and Liu et al differ in their perspectives of vaccine efficacy reflects the unease felt in sectors of the medical and scientific community. It is undeniable that there is a persuasive counternarrative to the 'safe and effective'[2] mantra that has accompanied the promulgation of COVID-19 mRNA and adenovirus DNA vaccines.

The perspective that primary doses of nucleic-acid vaccines encoding the SARS-CoV-2 spike protein have been effective in reducing hospitalisation and deaths during the COVID-19 pandemic is confounded by postulated overstating of the results due to selection bias, and case counting window concerns,[3,4] as Dr Lataster notes.

The threat of a prescient COVID-19 pandemic drove the acceptance of only short-term, placebo-controlled trial data as being sufficiently reliable to mass vaccinate (major pharmaceutical companies producing COVID-19 vaccines eventually vaccinated almost all placebo subjects, ostensibly for fear of COVID-19 infection, and lost their control groups[5]). The shortcomings to scientific integrity are now recognised.[6]

Other studies have indicated a negative effect of supernumerary vaccine dosing in the event of a new strain (Omicron) arising.[7] Efficacy waned until it was lower among those receiving a booster than those with only primary immunisation, likely due to immunological imprinting gearing the immune response to a pre-Omicron challenge.[7]

A proper explanation is needed for purported limitations in COVID-19 vaccine effectiveness. All-in-all, a 'back-to-first principles' analysis of vaccine efficacy is apposite.

Do vaccines protect against long COVID?

In view of the association of COVID-19 vaccination with postural orthostatic tachycardia syndrome (POTS) onset, it is appropriate that Drs Liu et al draw to attention the evidence derived from a meta-analysis of large datasets suggesting vaccination protects against long COVID (refer to references 10–13 in the letter by Drs Liu et al). However, Edwards and Hamilton[8] commenting on the review by Byambasuren et al,[9] which lists 17 observational studies, 12 looking at the effect of vaccination before COVID-19 infection and five looking at the effect after COVID-19 infection, noted 'many studies used symptoms coded by the International Classification of Diseases, 10th revision (ICD-10), rather than patient-reported symptoms of long COVID'. Although this approach allows large datasets to be analysed remotely, we cannot assume that an ICD-10 code reflects the lived experience of patients with long COVID. Another limitation was inconsistency in the long COVID definition between the studies, and whether a definition was provided at all. Differing duration of symptoms of long COVID can represent a different disease syndrome to that captured in the World Health Organization's definition.[10] Additionally, as with many observational studies on vaccination, the study had clear potential confounders, with those patients who take up vaccination being generally healthier than those who do not (the so-called healthy vaccine effect)'. The lack of consensus diagnostic criteria or standardised outcome measures are exacerbated by the recent determination of long COVID heterogeneity defined by serum proteomic profiles and specific inflammatory pathways.[11] Similar concerns pertain to the other dataset reviews cited by Drs Liu et al in support of vaccination preventing long COVID.

The salient point is that a resolution of the issues around vaccine efficacy remains paramount.

Vaccine adverse effects

Drs Liu et al point to evidence derived largely from multicountry, meta-analysis of data that vaccination with COVID-19 vaccines has few serious pathological sequelae (myocarditis, pericarditis, thrombosis with thrombocytopenia syndrome [TTS]) (refer to references 7–9 in the letter by Drs Liu et al). This approach to demonstrate relative safety raises concerns. It involves heterogeneity in data collection, quality and reporting standards across participating countries, varied vaccination strategies, differing prioritisation of vaccine recipients and difference in pre-existing health conditions. In lumping together vaccine recipients of all ages, safety signals are ignored or underreported in some subgroups (eg in men aged <40 years receiving two or more doses of vaccine).[12] Adverse events do not affect all populations equally. Subclinical adverse events might not appear in electronic records, or adverse events might be misinterpreted in an absence of intensive investigation.[13]

Meanwhile, spike protein pathogenicity, whether originating from vaccine nucleic acid or from SARS-CoV-2 infection, is being unravelled by molecular biology and pathophysiology investigations.[13] Studies support 'unprecedented high rates of adverse events' and cite 'evidence for widespread harms of... COVID-19 mRNA and adenovector DNA vaccines'.[14]

Adverse event data from official pharmacovigilance databases underestimate the rates of serious adverse events (SAE) five- to 100-fold.[15]

A re-analysis of the of the Pfizer and Moderna phase III trials (posted at www.clinicaltrials.gov) showed the vaccines caused serious adverse events in comparison to a placebo.[16]

A Food and Drug Administration (FDA)–Pfizer report derived via freedom of information showed high rates of, and multiple organ systems affected by, toxicity issues not taken into account in deliberations culminating in market approval of the genetic vaccines ostensibly because they were treated as conventional vaccines (ie protein/peptide + adjuvant) and not as prodrugs.[14]

In light of these conflicting views, it is encouraging that a deep dive into the pathological and immunological sequelae of long-term persistence of spike protein mRNA and its protein products continues to gather pace (summarised in reference 14).

Recent studies are particularly relevant. Patterson et al report that the S1 and S2 spike proteins persist for many months in SARS-CoV-2-negative, post-COVID-19 vaccine recipients with post-acute sequelae of COVID-19 (PASC).[17] The amount of spike protein from the vaccine is likely many fold greater than that from infection with virus because of stability mutations introduced into the vaccine mRNA, and the tissue penetrance of spike protein mRNA into a far more diverse set of tissues than infection.[18]

Spike protein toxicity has been demonstrated in multiple studies,[19] and damage occurs in various tissues (primarily neurological, cardiovascular and reproductive).

Binding of the S1 spike protein to sialylated glycan-rich erythrocytes, platelets and endothelial cells triggers blood clotting and related morbidities.[20] Prolonged exposure predisposes to clonal deletion or anergy of cognate immune response CD4 and CD8 T-cells and underlies the IgG1-to-(non-neutralising) IgG4 antibody class switch, which also induces immune tolerance through various pathways including induction of immunosuppressive cytokines and perturbation of complement function.[21] Spike protein is a novel intracellular 'foreign antigen' processed through the major histocompatibility complex class 1 pathway for 'non-self' recognition, ergo, autoimmunity.

The carrier for synthetic mRNA vaccines, lipid nanoparticles, itself can be toxic and can translocate across cellular barriers allowing access to multiple tissues including the brain.[22]

As it is becoming clear that the SARS-CoV-2 spike protein is pathogenic, whether derived from the virus or derived from the mRNA and adenovector DNA vaccine, one might be persuaded that the 'more-is-better' approach applied to traditional peptide/protein vaccines might be quintessentially flawed when applied to boosting with nucleic acid vaccines.

Overall, there are lingering concerns that a sober evaluation of COVID-19 vaccine effectiveness and safety has not been made. On both these issues, informed opinions are poles apart, and there is scant evidence of a continuum between them. The issue will not be resolved until the science is understood. This is a less-than-satisfactory scenario in which to recommend COVID-19 vaccination for everyone eligible for prevention of primary SARS-CoV-2 infection and disease, and for its application to long COVID.

Concerns among health providers and sufferers

Dr Murnane expresses one GP's concerns about vaccination and spike protein-associated pathologies. Similar concerns have been echoed by other GPs in response to the Viewpoint article. For example,

> (Long COVID is...) *a huge problem and one for which the GP cohort has little to offer apart from supportive measures. Even the special Long COVID clinics are limited in the assistance they can provide to sufferers. The toll on lives and families is nothing short of a tragedy. I have no doubt now, having witnessed it, that long COVID can be a side effect of the COVID vaccination.* (GP, Melbourne, Vic; R. Tindle pers. obs.)

and

> ..... *I had my alarm bells going from the very start but now you* (and others) *have confirmed what I knew. It is really making an impact amongst my patients who are alerting me to it as well as my colleague GPs...* (GP, Sydney, NSW; R. Tindle pers. obs.)

Persecution of health practitioners by the Australian Health Practitioner Regulation Agency (AHPRA) for challenging the official governmental position on the COVID-19 pandemic response is alarming. As are the anecdotal reports of doctors under-reporting COVID-19 vaccine adverse events to the Database of Adverse Events Notifications (DAEN) for fear of reprisal (R. Tindle, pers. obs).

A rigorous qualitative analysis of the lived experiences of the large number of sufferers (including general practitioners [GPs] and other health professionals) on digital long COVID support platforms[23–25] reporting post-vaccination symptoms, which transcend the 'few rare types of events ... linked to COVID-19 vaccines (see the letter by Drs Liu et al)' might add traction in the debate. Many sufferers report that their GPs had advised of a possible 'Long Vax(x)' aetiology of their condition (note that, until recently, posts implicating COVID-19 vaccines were removed by the site moderators).

A way forward

Open discussion, the very stuff of scientific enquiry, is stultified. It can only do harm to a timely understanding of how best the COVID-19 situation should be handled, of genetic vaccines, and of response to putative future pandemics.

Drs Lataster, Liu et al and Murnane contribute in important ways to this discussion.

Should trends in the emerging data persist, it is reasonable to ask whether the benefits of the current strategy for repetitive COVID-19 vaccination outweighs its risks for individual informed consent and for public policy. Not every age group demonstrates net harm (eg the elderly derive net benefit). But to recommend doing net harm in certain age groups (eg young men) is a questionable practice. It might be appropriate that the Federal Government's proposal of repetitive vaccination for such groups[26] be revisited.

It is pertinent that in a parliamentary debate on 18 April 2024 in the UK House of Commons (in which the Viewpoint article[1] was cited), the motion was carried by the House for a 'COVID-19 enquiry into vaccines and therapeutics as soon as possible'. It would be appropriate were the vaccine issue addressed in the forthcoming Commonwealth Government COVID-19 Response Inquiry[27] and/or by the proposed Australian Senate COVID-19 Royal Commission.

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