

Characterising long COVID-like COVID-19 vaccine reactions

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Declarations: CC is the co-founder of the largest UK COVID-19 vaccine injured support group (UKCVFamily). HAC is a member of UKCVFamily. No other declarations or competing interests.

Funding: Survey software was paid for by NHS Grampian Endowment Funds

Data availability: Data are available from: <https://doi.org/10.5281/zenodo.10576421>. Code for Supplementary Figures S4a-i can be found here: <https://github.com/dylanlikelihood/Vaccine/tree/main>

Abbreviations: ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CAM, complementary and alternative medicine; CoQ10, coenzyme Q10; CRP, C-reactive protein; DOAC, direct oral anticoagulant; EBV, Epstein-Barr virus; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; GP, general practitioner; HbA1c, glycated haemoglobin; HBOT, hyperbaric oxygen therapy; HDL, high density lipoprotein; HELP, heparin induced extracorporeal LDL precipitation; HPV, human papillomavirus; Ig, immunoglobulin; IL, interleukin; IVIG, Intravenous immunoglobulin; LDL, low density lipoprotein; LDN, low dose naltrexone; LFT, lateral flow test; MCAS, mast cell activation syndrome; ME, myalgic encephalomyelitis; MMA, methylmalonic acid; MPO, anti-myeloperoxidase antibody; MRI, magnetic resonance imaging; MTHFR, methylenetetrahydrofolate reductase; NAC, N-acetyl cysteine; NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; PCP, primary care provider; PCR, polymerase chain reaction; PFTs, pulmonary function tests; POTS, postural orthostatic tachycardia syndrome; PR3, anti-proteinase 3 antineutrophil cytoplasmic antibodies; QSART, quantitative sudomotor axon reflex test; QST, quantitative sensory testing; RBC, red blood cell; RF, rheumatoid factor; SFN, small fibre neuropathy; SpO2, blood oxygen saturation; SvO2, venous oxygen saturation; TS HDS, trisulfated-heparin disaccharide; V/Q, ventilation/perfusion; VEGF, vascular endothelial growth factor; VITT, vaccine-induced immune thrombocytopenia and thrombosis; WBC, white blood cell

Abstract

Background: Chronic adverse reactions to COVID-19 vaccinations, which present similarly to long COVID, have thus far been poorly acknowledged, with little public awareness, and lack of clinical guidance. However, such reactions are increasingly being recognised in the academic literature

Aim: To characterise long COVID-like vaccine adverse reactions.

Methods: Cross-sectional online survey asking about symptoms, test results, diagnoses, and treatments in adults reporting with chronic symptoms starting shortly after a COVID-19 vaccine. Data were analysed for the whole sample, as well as comparing those who report chronic injury from a vector *versus* mRNA vaccine. Five cluster analyses were done to identify participant or symptom clusters.

Results: Participants reported good health prior to vaccination and poor health after, where they typically had a high symptom burden, with many respondents experiencing > 20 symptoms. The most commonly reported symptoms were fatigue, cognitive dysfunction, and exercise intolerance, with 11 pre-specified symptoms having a higher prevalence after a vector vaccine compared to mRNA recipients. Most test results came back normal, though commonly reported abnormalities included haematinics, D-dimer, anti-nuclear antibody, C-reactive protein, cardiac tests, and research-only tests. Six tests were more frequently reported as abnormal after a vector than mRNA vaccine, e.g. high D-dimer. Post-vaccine syndrome, dysautonomia, anxiety/mental health related, postural orthostatic tachycardia syndrome (POTS), and tachycardia were the most common diagnoses, often taking > 6 months to receive a diagnosis. Treatments targeting mast cell activation, inflammation, and POTS were most frequently reported as helpful. Cluster analyses did not yield clearly defined subgroups. Participants reported an overall poor healthcare experience.

Conclusion: Although there was high heterogeneity in clinical presentations and response to treatments, the findings are in accordance with our current understanding of long COVID and related illnesses such as myalgic encephalomyelitis. Neuroimmune dysfunction and coagulopathy seem to underlie many of these COVID-19 vaccines reactions, though biomedical research is needed to confirm this inference and offer effective treatments.

Introduction

The SARS-CoV-2 pandemic posed an immediate global threat that rapidly needed addressing. With this came an urgent need to vaccinate the population *en masse* to reduce disease burden, unlike previous vaccination campaigns, which have been rolled out over time. Data from phase 3 trials of three of the main vaccines given in the UK (Pfizer BNT162b2, Moderna mRNA-1273, AstraZeneca ChAdOx1 nCoV-19) showed up to ~95 % efficacy against symptomatic infection (Baden et al., 2021; Falsey et al., 2021; Polack et al., 2020). Alongside high efficacy, acceptable safety profiles were also shown.

However, some trial participants experienced long COVID-like vaccine reactions (Healy et al., 2023). Since these participants did not complete the trial, their reactions were not reported for safety assessments by approval bodies, and since trials are not powered to detect reactions occurring in (e.g.) 1 in > 10,000 vaccinees, it would likely have been deemed unclear whether the vaccine caused the illnesses that followed (Healy et al., 2023).

Since the rollout, several side effects are now established that were not shown in trials, such as myo/pericarditis from mRNA vaccines, and vaccine-induced immune thrombocytopenia and thrombosis (VITT) from viral vector vaccines. In patient support groups, long COVID-like reactions are the predominating problem patients report post-vaccine, yet relatively little research has gone into these and they are not formally recognised.

Long COVID is a constellation of > 200 possible symptoms that occur after SARS-CoV-2 infection (Davis et al., 2021). A range of mechanisms have been reported to contribute to these symptoms, such as dysbiosis (Davis et al., 2023), autoimmunity (Davis et al., 2023; Perumal et al., 2023), mast cell activation syndrome (MCAS) (Perumal et al., 2023; Sumantri and Rengganis, 2023), dysautonomia (Kwan et al., 2022; Perumal et al., 2023), coagulopathy (Kerr and Carroll, 2023; Turner et al., 2023), spike protein/viral persistence (Davis et al., 2023; Patterson et al., 2021), and endocrine dysfunction (Szczerbiński et al., 2023). In addition, up to ~20 % of long COVID patients experience symptomatic worsening after vaccination (Grady et al., 2024; Strain et al., 2022; Tsuchida et al., 2022).

Patients in support groups have been finding similar pathologies post-vaccine. Increasingly research and clinical experience is supporting patient experience, including growing evidence for autoimmunity (Guo et al., 2023), persistent spike protein (Patterson et al., 2022), coagulopathy (Kerr and Carroll, 2023; Talotta and Robertson, 2021; Turner et al., 2023), dysautonomia (Kwan et al., 2022), and endocrine dysfunction (Zhao and Wu, 2022). Indeed, prior to COVID-19, other vaccines had also been associated with long COVID-related pathologies, such as MCAS (Afrin et al., 2022) and dysautonomia (Blitshteyn et al., 2018; Gøtzsche and Jørgensen, 2022; Jørgensen et al., 2020; Mehlsen et al., 2022).

Acceptance of long COVID-like vaccine reactions is rising, both in scientific mainstream media and in research (Carroll and Deans, 2022; Couzin-Frankel and Vogel, 2022; Deans et al., 2022; Finsterer, 2022a; Kerr and Carroll, 2023; Krumholz et al., 2023; Patterson et al., 2022; Schieffer and Schieffer, 2022; Scholkmann and May, 2023; Turner et al., 2023; Vogel and Couzin-Frankel, 2023). Nonetheless, patients still find themselves in an evidence void, whereby clinicians are unclear about how to investigate or treat patients. This paper therefore aims to characterise these patients to understand symptom clusters, test results, diagnoses, and potential treatments.

Methods

Study design and sample

This was a cross-sectional patient-initiated and patient-led survey of adults (aged ≥ 18 y) who had a suspected or confirmed vaccine injury that presented similarly to long COVID, starting within 3 months of vaccination (in line with long COVID onset). Recruitment was via public social media and private support groups (primarily Twitter and Facebook), and people were encouraged to share the survey. REACT19 (a patient support network) also included a link to the survey on their website and aided with distribution via their social media channels. A bespoke online survey was created for this study using Online Surveys (<https://www.onlinesurveys.ac.uk/>). The survey was open from 9 June 2022 to 24 July 2022. Because there is associated trauma with reliving medical history, most of the questions were optional and had a “not sure/prefer not to say” option. All participants gave informed consent to participate after reading the participant information, and the survey would not continue if consent was not given.

The questionnaire had several sections addressing different aspects of vaccine injury:

Participant characteristics and demographics: Included age, gender, information on pre-vaccine health, COVID-19 infections, vaccine brands, and acute vaccine-related symptoms. To help maintain anonymity, questions were categorised (e.g. age brackets rather than actual age).

Symptoms: Included 53 pre-specified symptoms based on accounts from the vaccine injured community, symptom severity (at its worst), time to onset, and an open-ended question to include other symptoms and triggers.

Tests: Included 132 pre-specified tests based on our experience in the vaccine injured community, asking who did the tests, whether the result was within the reference range (on first measurement), whether the result stayed stable in follow-up measurements, the first time it was measured, and an open-ended response for other tests.

Diagnoses: Included 39 pre-specified diagnoses based on accounts from the vaccine injured community, whether participants agreed with the diagnosis, whether they thought they had it (but had not received a diagnosis), time to diagnosis, who made the diagnosis, and an open-ended question for other diagnoses.

Treatments: Included 39 pre-specified treatments based on accounts from the vaccine injured community, asking who prescribed it, when was it started, how many times it was tried, how long it was tried (the longest time), whether it helped or had side effects, whether it was taken with other treatments, and an open-ended question for other treatments tried.

Participant experience: Included questions about their experience with and perceptions of healthcare, how this compared to alternative healthcare providers, and an open-ended question in which they could tell their story (these data are being analysed separately, but are available in the published dataset). We did this because accounts from the vaccine injured community suggest that patients not only feel unheard, but there have been active attempts at censorship. We felt their voices and stories deserved to be heard.

Analysis

Data were analysed using Stata (StataSE 64, version 15.1), R (version 4.3.0) and Python (version 3.11.1) statistics software. Descriptive data are presented as number (n) and percentage (%) of respondents. We additionally split the analyses for symptoms, tests, diagnoses, and treatments according to vaccine type (mRNA *versus* vector vaccine; this necessitated excluding n = 1 who was injured from Novavax), and used χ^2 to determine whether there were imbalances. We acknowledge the limitations of non-random sampling in interpreting our χ^2 results.

In order to understand participant clusters, we ran k-modes in Python which is designed for clustering categorical variables. We ran five clustering models: (i) including all relevant data from the dataset (symptoms, test results, diagnoses, treatments); (ii) symptoms (maintained in their original categories defining severity); (iii) symptoms binary (i.e. whether they had a symptom at any severity *versus* not having that symptom); (iv) symptoms binary for mRNA vaccine recipients; (v) symptoms binary for vector vaccine recipients. Following this, we regressed the cluster coefficients of the binary symptoms model (all vaccines) to test results (tests that were reported by > 20 respondents). Our aim was to try and identify whether there were symptom clusters, and whether these clusters could predict other aspects of vaccine injury, with a particular focus on abnormal test results as this can help clinicians.

The study did not meet requirements for NHS ethical approval as it was a completely anonymised online survey, participants were not identified in the context of their past or present use of NHS services, and it was advertised publicly (rather than via NHS systems), as advised by the lead author's NHS ethics board at the time. Data are available from: <https://doi.org/10.5281/zenodo.10576421>.

Results

Participant characteristics

A total of 230 participants reporting a chronic adverse reaction to a COVID-19 vaccine completed the survey. Most participants were aged < 46 y at the time of vaccination. The majority of respondents identified as female (70 % *versus* 28 % male and 2 % non-binary/other), and were predominantly white (93 % *versus* 3 % mixed or multiple ethnic groups, 2 % Asian, and 1 % other). According to body mass index, 65 % were in the healthy range (18.5-24.9 kg/m²), 22 % had overweight (25.0-29.9 kg/m²), 6 % had obesity (≥ 30.0 kg/m²), and 5 % were underweight (< 18.5 kg/m²). Most (65 %) had never smoked, 8 % were current smokers, and 27 % were former smokers (**Table 1**).

Table 1. Participant characteristics

Characteristic	Answer category	n (%)
Part of a support group	Yes	142 (62)
Age bracket (y)	18-25	13 (6)
	26-30	17 (7)
	31-35	34 (15)
	36-40	38 (17)
	41-45	42 (18)
	46-50	30 (13)
	51-55	18 (8)
	56-60	22 (10)
	61-65	8 (3)
	66-70	4 (2)
	71-75	2 (1)
	> 75	2 (1)
Gender	Female	162 (70)
	Male	64 (28)
	Non-binary / other	4 (2)
Same gender as birth	Yes	223 (97)
	No	4 (2)
	Prefer not to say	2 (1)
Ethnicity	Asian	4 (2)
	White	215 (93)
	Mixed or multiple ethnic groups	6 (3)
	Other	3 (1)
	Prefer not to say	2 (1)
BMI status	Underweight	12 (5)
	Healthy weight	150 (65)
	Overweight	51 (22)
	Obese	14 (6)
	Prefer not to say	3 (1)
Smoking status	Current smoker	18 (8)
	Former smoker	63 (27)
	Never smoked	149 (65)

Health pre-vaccine

At the time of vaccination, most respondents reported being in generally good health (**Figure 1**). Prior to vaccination, 39 (17 %) participants suspected they had a pre-existing (non-autoimmune) health condition and 22 (10 %) suspected they had dysautonomia, but these had not been diagnosed. Most common diagnosed conditions prior to vaccination were musculoskeletal (15 %), gastrointestinal (14 %), autoimmune (10 %), and other (14 %) problems (**Table 2**). Overall, 71 % stated their health prior to vaccination was “excellent” or “very good”, compared to 9 % who reported it being “poor” or “very poor” (**Figure 1**).

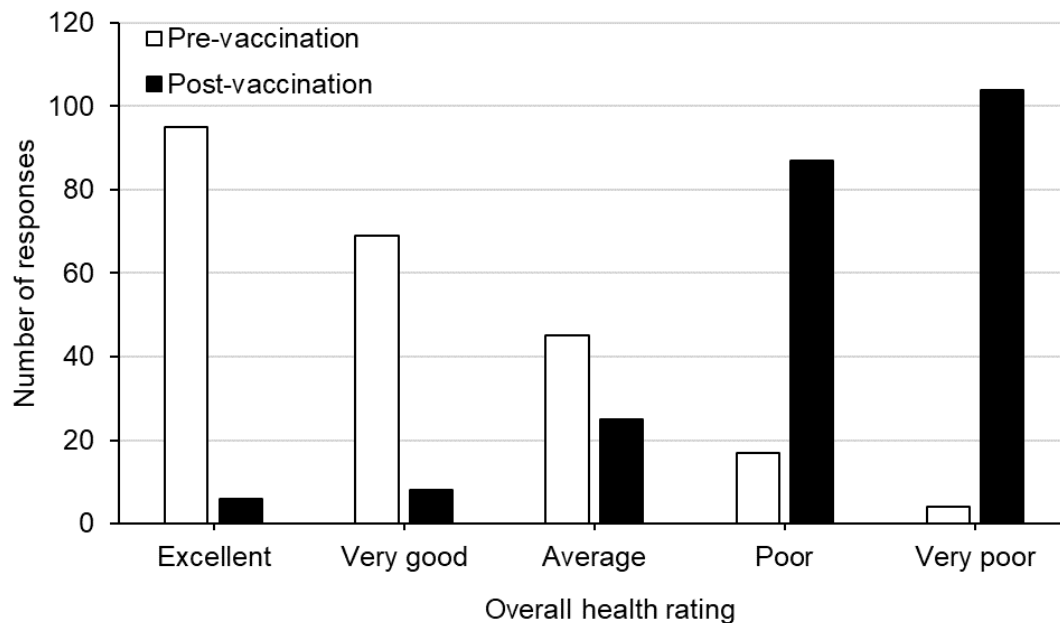


Figure 1. Overall health ratings of respondents (n = 230) pre- (white bars) *versus* post- (black bars) vaccination

Table 2. Reported diagnosed or suspected health conditions prior to vaccination

Condition	Diagnosed n (%)	Suspected but not diagnosed n (%)	Medication use n (%)
Autoimmunity	24 (10)	15 (6)	11 (5)
Cardiovascular problems	8 (3)	10 (4)	10 (4)
Dysautonomia	10 (4)	22 (10)	5 (2)
Endocrine/reproductive problems	21 (9)	13 (6)	16 (7)
Gastrointestinal problems	33 (14)	28 (12)	15 (7)
Metabolic problems	9 (4)	9 (4)	7 (3)
Musculoskeletal problems	35 (15)	17 (7)	21 (9)
Neurological problems	11 (5)	18 (8)	8 (3)
Other immune condition	4 (2)	39 (17)	6 (3)
Other pre-existing problems	33 (14)	13 (6)	20 (9)
Systemic problems	23 (10)	25 (11)	8 (3)

COVID-19

At the time of taking the survey, 50 % reported no known COVID-19 infection. 32 % had ≥ 1 confirmed (by polymerase chain reaction [PCR] or lateral flow test [LFT]) COVID-19 infection, and the rest suspected they had had COVID-19. Of those who had COVID-19, 29 % reported getting long COVID, whilst 22 % were not sure. Whilst COVID-19 infections typically occurred after vaccination (51 %), 16 % had an infection both pre- and post-vaccine, 32 % were infected pre-vaccine, and 2 % had COVID-19 around the same time as their vaccine. COVID-19 tended to make vaccine-related symptoms worse (38 %), with a minority (9 %) reporting improvement, 17 % reported mixed effects on symptoms, and 30 % reported no change. In those who reported having long COVID prior to vaccination ($n = 31$), none reported improvement to their symptoms post-vaccine, whilst 81 % reported symptom worsening (**Supplementary Material Table S1**).

Vaccine

At the time of the survey, it had been over one year since the time of vaccination for 61 % of respondents. The majority had Pfizer (47 %), followed by AstraZeneca (35 %), Moderna (15 %), Janssen (3 %), and Novavax (1 %). 37 % of participants had one, 35 % had two, 25 % had three, and 2 % had > 3 vaccines. 63 % of those who had > 1 vaccine had a different brand to their first vaccine. Of those who had another vaccine after getting ongoing symptoms from a previous vaccine ($n = 111$), 49 % got worse, 23 % had no notable change, 9 % had a mixed response (e.g. some symptoms got better, others got worse), 19 % were not sure, and 1 % had improvement. Time between vaccines 1 and 2 was typically between 2 weeks to 3 months (**Supplementary Materials Table S2**).

49 % of participants had no notable acute flu-like or similar expected reaction to the vaccine. Of those who had an acute reaction, 31 % reported this as being “strong”, 8 % “moderate”, and 10 % “mild”. A total of 175 unique batch numbers were reported. Fifty-three batch numbers were reported by > 1 participant, with batch 4120Z003 being reported the most (by six participants). Full information is given in the **Supplementary Material Section S1**.

Health post-vaccine

After vaccination, 83 % reported their health being “poor” or “very poor” (**Figure 1**), with only 6 % reporting “excellent” or “good” health. The symptoms that became chronic started within 24 hours in 34 % of respondents; within 1-7 days in 34 %; within 1-4 weeks in 27 %; and started after 1 month in 4 %. Symptoms most typically fluctuated (highly fluctuant 13 %; moderately fluctuant 34 %; mildly fluctuant 20 %), with 10 % reporting steady improvement, 8 % reporting a steady decline, and 13 % reporting no notable change. Symptom fluctuations had a clear pattern for 23 % of respondents, an unclear or inconsistent pattern for 40 %, and no pattern for 30 % (**Supplementary Materials Table S3**).

Of those to whom the question applied ($n = 176$), most respondents (86 %) required time off due to their vaccine-related symptoms. Of those who answered the follow-on question ($n = 152$), 27 % had to stop working, 34 % required < 6 months off, and 39 % required > 6 months off. 78 % (of $n = 139$ that answered) required workplace adjustments (**Supplementary Materials Table S3**).

95 % of respondents reported still having symptoms at the time of the survey; 10 % had had symptoms for < 6 months, 32 % for 6-12 months, and 58 % for > 12 months (**Supplementary Materials Table S3**).

Symptoms

We pre-specified 53 symptoms; 49 % of respondents stated they also experience ≥ 1 other symptom that was not pre-specified. Of the 53 provided, 50 % of participants experienced ≥ 20 symptoms. The most common symptoms were fatigue (87 %), cognitive dysfunction (80 %), exercise intolerance (71 %), and light-headedness (70 %). Of the pre-specified symptoms, the least common were seizures (7 %), nailfold haemorrhage (10 %), paralysis (12 %), and hallucinations (12 %). **Figure 2** shows symptoms and their severity (“mild”, “moderate”, “severe”, “extreme”) at their worst.

Symptoms typically had an onset of days to weeks, though some symptoms tended to take longer to develop in more participants, such as hair loss, nail problems, and weight changes (**Supplementary Material Figure S1**). When comparing symptoms between mRNA and vector vaccines, some potential imbalances were found (**Table 3**); all imbalances showed a higher prevalence with vector vaccines.

Table 3. Symptom imbalances according to vaccine type (n = 229)

Symptom	Vector (n = 86)	mRNA (n = 143)	p-value
Hallucinations n (%)	38 (44)	43 (30)	0.030
Sensory sensitivities n (%)	41 (55)	57 (40)	0.029
Vision problems n (%)	51 (59)	63 (44)	0.025
Spasms n (%)	32 (37)	32 (22)	0.015
Joint inflammation n (%)	44 (51)	45 (31)	0.003
Blood pressure problems n (%)	43 (50)	52 (36)	0.043
Paralysis n (%)	17 (20)	10 (7)	0.004
Fine motor skill problems n (%)	37 (43)	28 (20)	< 0.001
Tremors n (%)	39 (45)	39 (27)	0.005
Speech problems n (%)	37 (43)	41 (29)	0.026
Weakness n (%)	64 (74)	88 (62)	0.046

Data analysed using χ^2

For each symptom, participants were asked whether the symptom was fluctuant, remaining roughly stable, or changing linearly. Across all symptoms, 44 % of participants reported fluctuations, 37 % reported linear change (improvement or decline), and 20 % reported symptom stability. **Supplementary Material Figure S2** shows symptom fluctuations in more detail. We also asked whether there was a trigger for each listed symptom; across all symptoms, 41 % of responses reported having a trigger, 33 % did not have a trigger, and 27 % were not sure. The most common symptoms to have triggers were fatigue, tachycardia, anxiety, food allergies/sensitivities, and nailfold haemorrhages, and the least likely were hair loss, brain zaps, bruising, taste changes, and twitching (**Supplementary Material Figure S3**). Triggers included fatigue, periods, relapses, physical activity, stress, temperature, food, sleep, and infection (see **Supplementary Material Figures S4a-i** for a breakdown of how triggers impacted pre-specified symptoms).

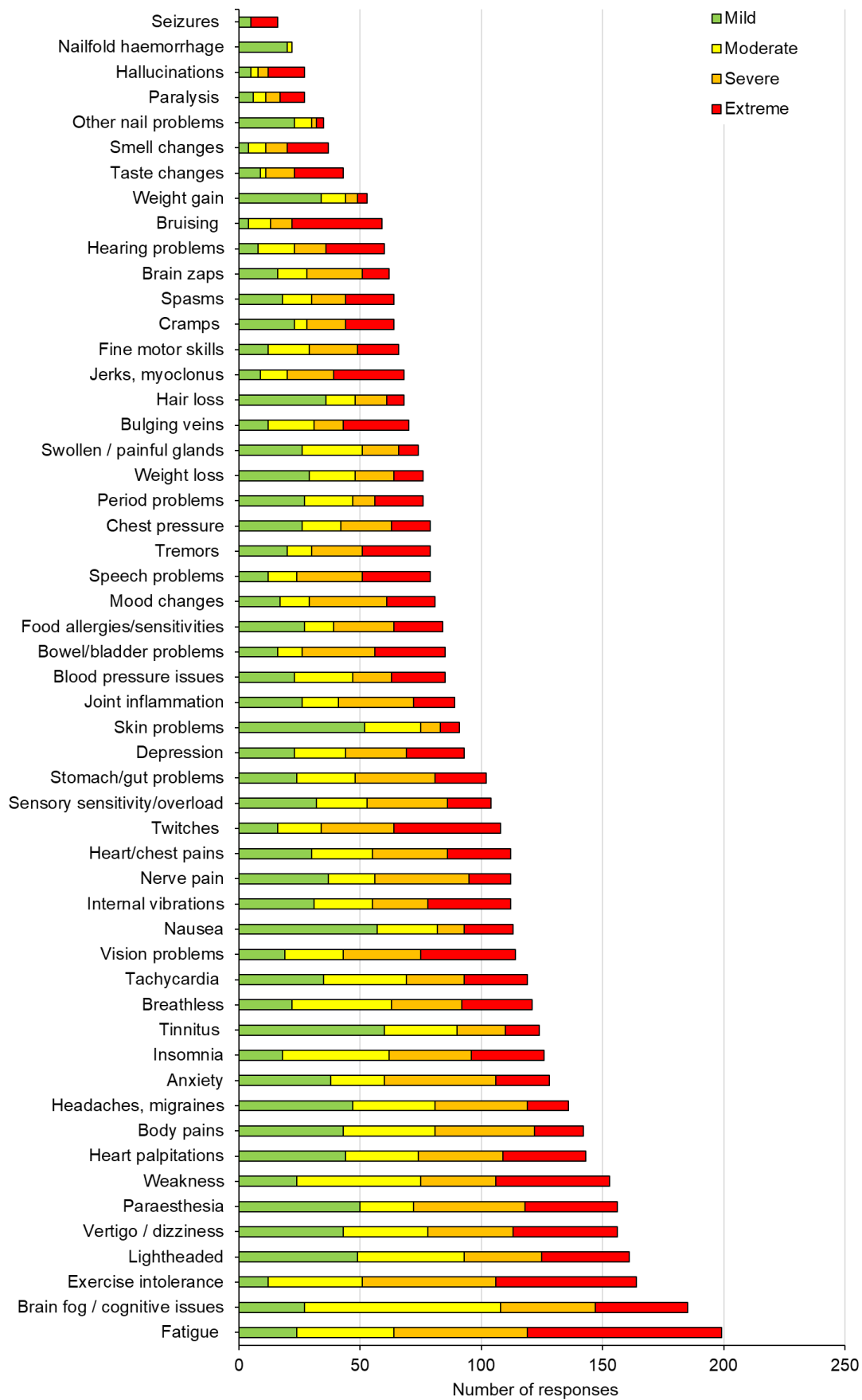


Figure 2. Symptom severity at worst

Tests

We pre-specified 132 possible tests participants may have had. 30 respondents stated they had not had any tests at the time of the survey. Another 72 indicated they did not know the name of and/or results for at least one of the tests they had; of these participants, $n = 31$ indicated at least some of the tests they did not know the name of were outwith the reference range. 97 participants used the open text at the end of the section to describe other tests they had done.

In total, participants reported having 3,344 tests (based on the 132 tests we pre-specified). Most (83 %) were done by a conventional medical practitioner (e.g. a general practitioner [GP]); 13 % were paid for privately or done by the participant; and 2 % were done by complementary and alternative medicine (CAM) providers.

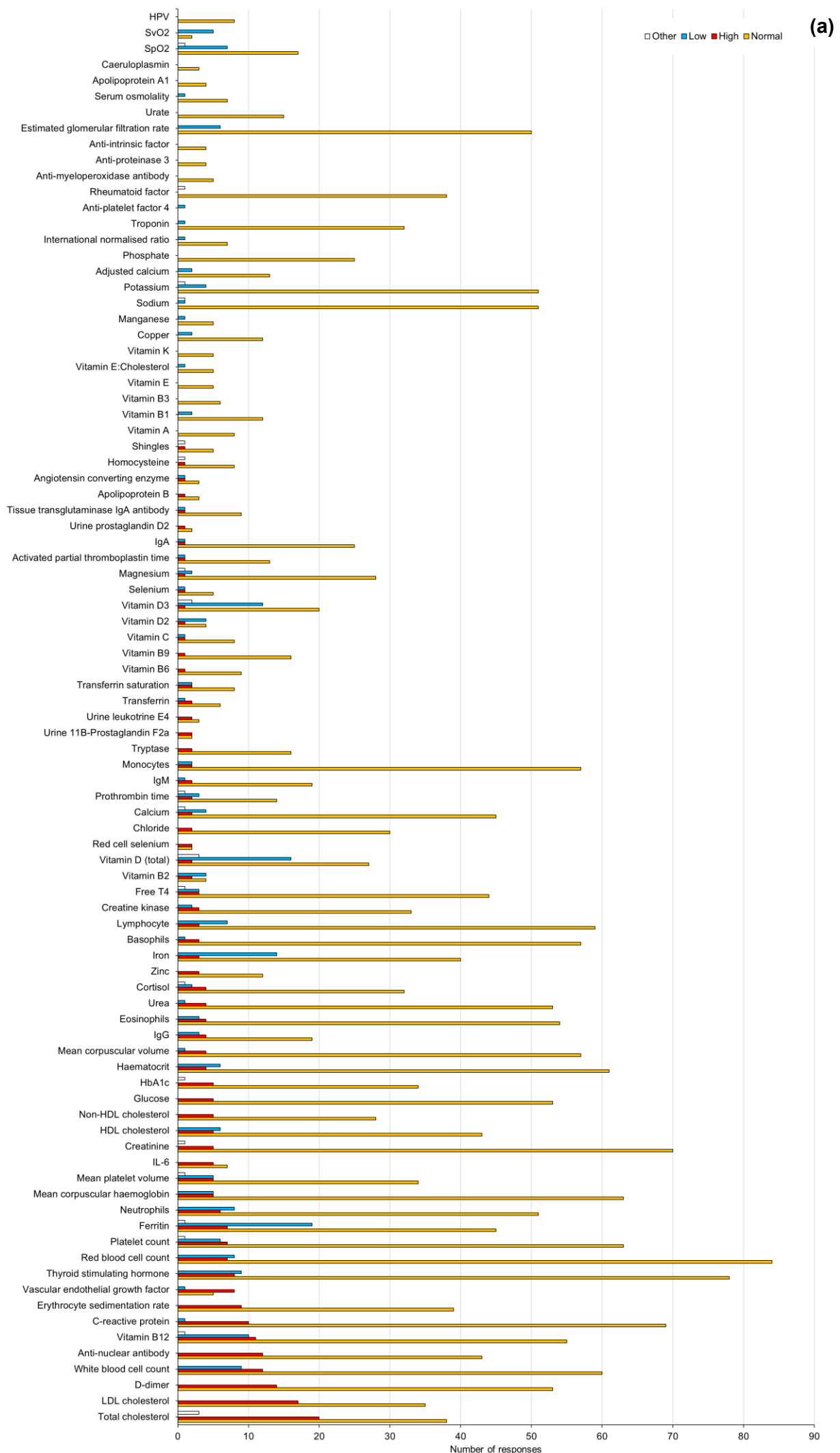
Due to differences in reference ranges and units, we asked only whether results were within reference ranges or not. Results are summarised in **Figure 3(a,b)**. Notably, the majority of test results were within normal ranges. Cytokine panels, microclots, and certain G-protein couple receptor autoantibodies (typically done in research or paid for privately) most reliably came back abnormal, though < 10 % of respondents had done these tests.

Whilst tests generally came back within the normal range, some results more commonly came back abnormal. B12, vitamin D, iron, ferritin, white blood cell count, oxygen saturations (SpO₂), and venous oxygen saturations (SvO₂) often came back low; B12, vascular endothelial growth factor (VEGF), D-dimer, anti-nuclear antibody (ANA), C-reactive protein (CRP), white blood cell count, and total and low density lipoprotein (LDL) cholesterol often came back high. Of those who tested reactivated pathogens, Epstein-Barr virus (EBV) often came back positive, and abnormalities were frequently found on echocardiograms, magnetic resonance imaging (MRI) (head) scans, electrocardiograms, tilt table tests, blood pressure monitoring, and Holter monitors.

In those who had a contrast dye with imaging ($n = 49$), 8 % had a mild severity acute (< 2 d) reaction; 4 % had a severe acute (< 2 d) reaction; 8 % had a severe chronic reaction; 4 % had a moderate severity chronic reaction; 69 % had no reaction; and 6 % were not sure. Numerically more reactions were reported by those who were injured by a vector vaccine ($n = 9$ vector *versus* $n = 3$ mRNA), and numerically more participants injured by mRNA vaccine reported no reaction to contrast dye ($n = 13$ vector *versus* $n = 21$ mRNA) ($p = 0.287$).

The majority of tests (~60 %) were done after 2 months of symptom onset (**Figure 4**), and most tests that were done earlier were basic tests (e.g. full blood count) which were less informative (**Supplementary Material Figure S5**). 19 % of pre-specified tests were done twice, and 29 % were done ≥ 3 times. On the whole, most tests (65 %) did not meaningfully change upon repeat testing, though repeat testing was not common (**Supplementary Material Figure S6**).

When comparing test results between mRNA and vector vaccines, some potential imbalances were found (**Table 4**); all imbalances showed a higher prevalence of an abnormal test result with vector vaccines, and a higher prevalence of normal test results with mRNA vaccines.



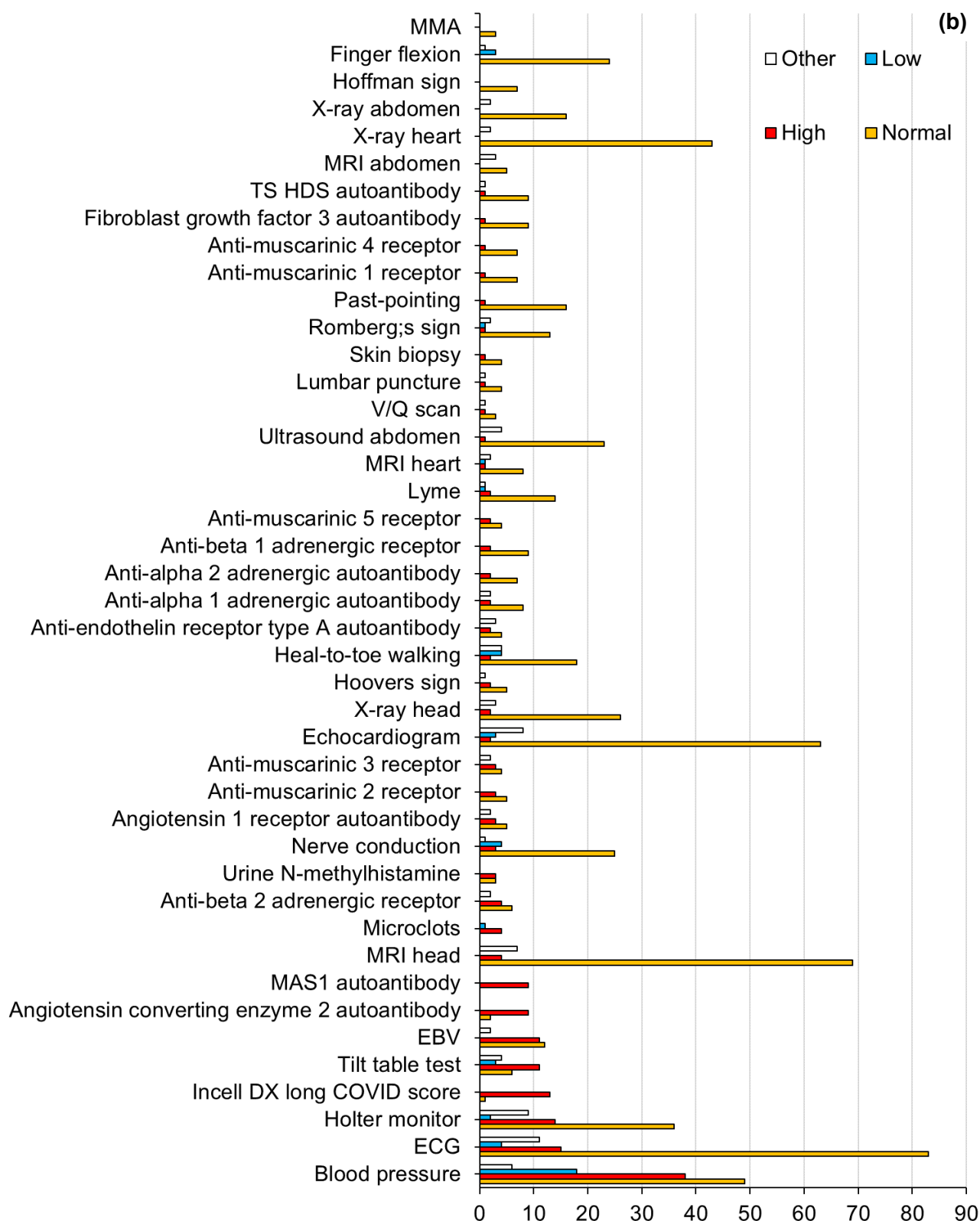


Figure 3. Standard clinical blood test **(a)**, and other clinical or research-only test **(b)** results. Abbreviations: EBV, Epstein-Barr virus; ECG, electrocardiogram; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; HPV, human papillomavirus; Ig, immunoglobulin; IL, interleukin; LDL, low density lipoprotein; MMA, methylmalonic acid; SpO₂, blood oxygen saturation; SvO₂, venous oxygen saturation; TS HDS, trisulfated-heparin disaccharide; V/Q, ventilation/perfusion. Due to an error in the survey, IgE was not asked about

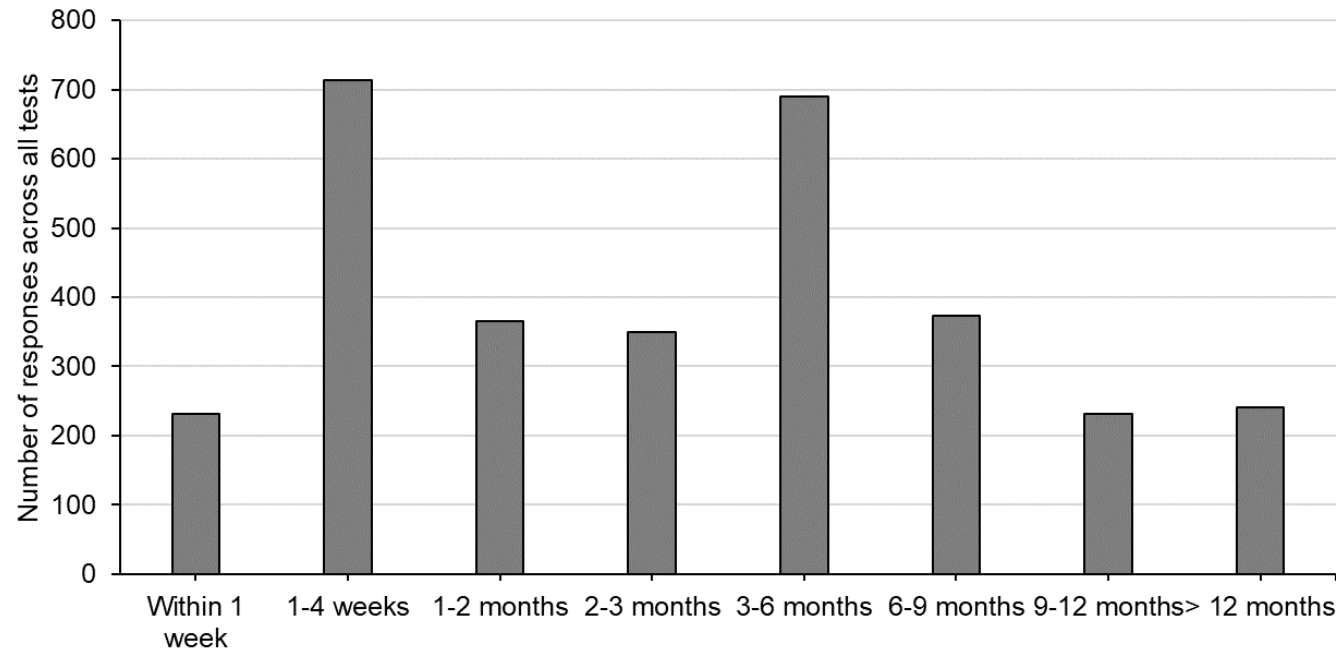


Figure 4. Timeframe in which tests were first run, from the time post-vaccine symptoms started

Table 4. Test result imbalances between vaccine types

Test	Vector (n = 86)					mRNA (n = 143)					p-value
	Normal	High	Low	Other	Not sure	Normal	High	Low	Other	Not sure	
D-dimer n (%)	15 (58)	9 (35)	-	-	2 (8)	38 (88)	5 (12)	-	-	-	0.009
RBC count n (%)	26 (65)	4 (10)	7 (18)	-	3 (8)	58 (94)	3 (5)	1 (2)	-	-	0.001
Haematocrit n (%)	11 (50)	3 (14)	5 (23)	-	3 (14)	50 (94)	1 (2)	1 (2)	-	1 (2)	< 0.001
Platelet count n (%)	15 (52)	4 (14)	5 (17)	1 (3)	4 (14)	48 (91)	3 (6)	1 (2)	-	1 (2)	0.002
WBC count n (%)	18 (58)	7 (23)	6 (19)	-	-	42 (81)	5 (10)	3 (6)	-	2 (4)	0.043
Urea n (%)	14 (67)	3 (14)	1 (5)	-	3 (14)	39 (95)	1 (2)	-	-	1 (2)	0.025

Data analysed using χ^2 . Abbreviations: RBC, red blood cell; WBC, white blood cell

Diagnoses

The survey provided a list of 39 pre-specified diagnoses. 98 respondents (43 %) reported having ≥ 1 formal diagnosis at the time of the survey. From the list of diagnoses we provided, participants reported a total of 529 diagnoses. Of the diagnoses given, participants did not agree with 27 % of them. 75 respondents reported having an additional formal diagnosis that was not included in the list. Participants reported a further total of 840 diagnoses they had not been diagnosed with but felt they had. Most diagnoses came from GPs/equivalent, followed by cardiologists (22 %), other medical doctors (20 %), and neurologists (17 %) (**Figure 5**), and it most commonly took 12-15 months to receive a diagnosis (**Figure 6**).

The most common diagnosis was post-vaccine syndrome (18 %), followed by dysautonomia (14 %), anxiety/mental health related (14 %), postural orthostatic tachycardia syndrome (POTS) (14 %), and tachycardia (14 %) (**Figure 7**). When comparing diagnoses between mRNA and vector vaccines, the only imbalance found was the diagnosis of “vaccine-induced long COVID” which occurred more frequently with vector vaccines (17 % *versus* 8 %; $p = 0.004$).

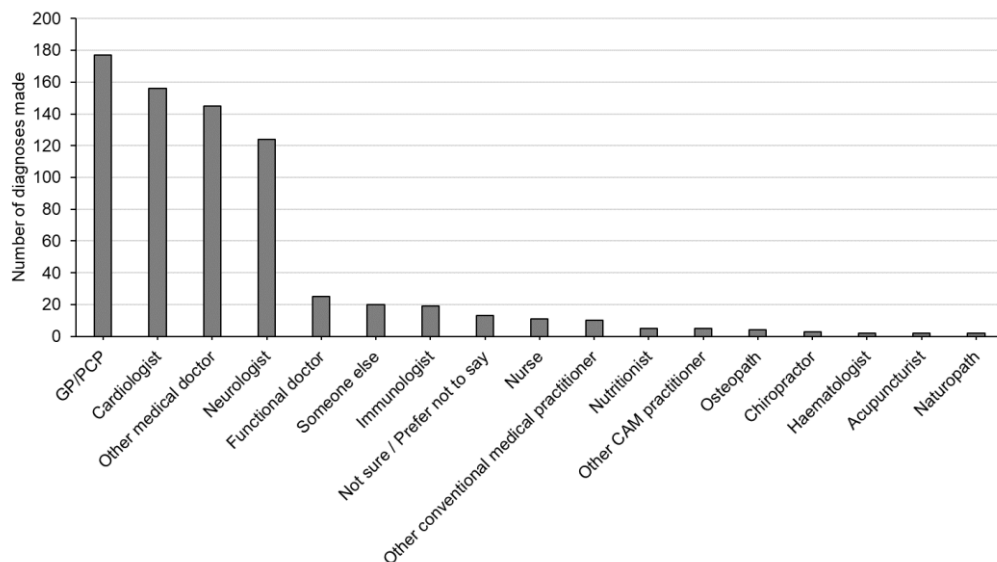


Figure 5. Number of diagnoses given by healthcare professionals. Abbreviations: CAM, complementary and alternative medicine; GP, general practitioner; PCP, primary care provider

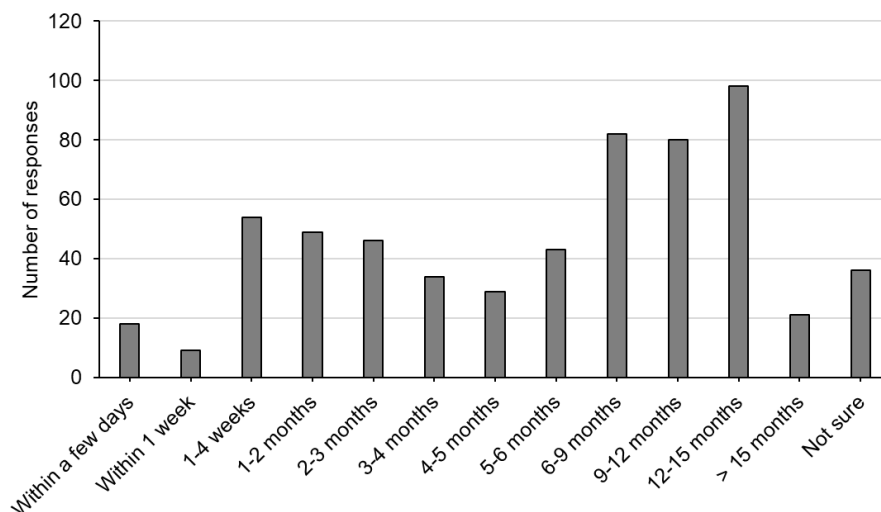


Figure 6. Time to diagnosis

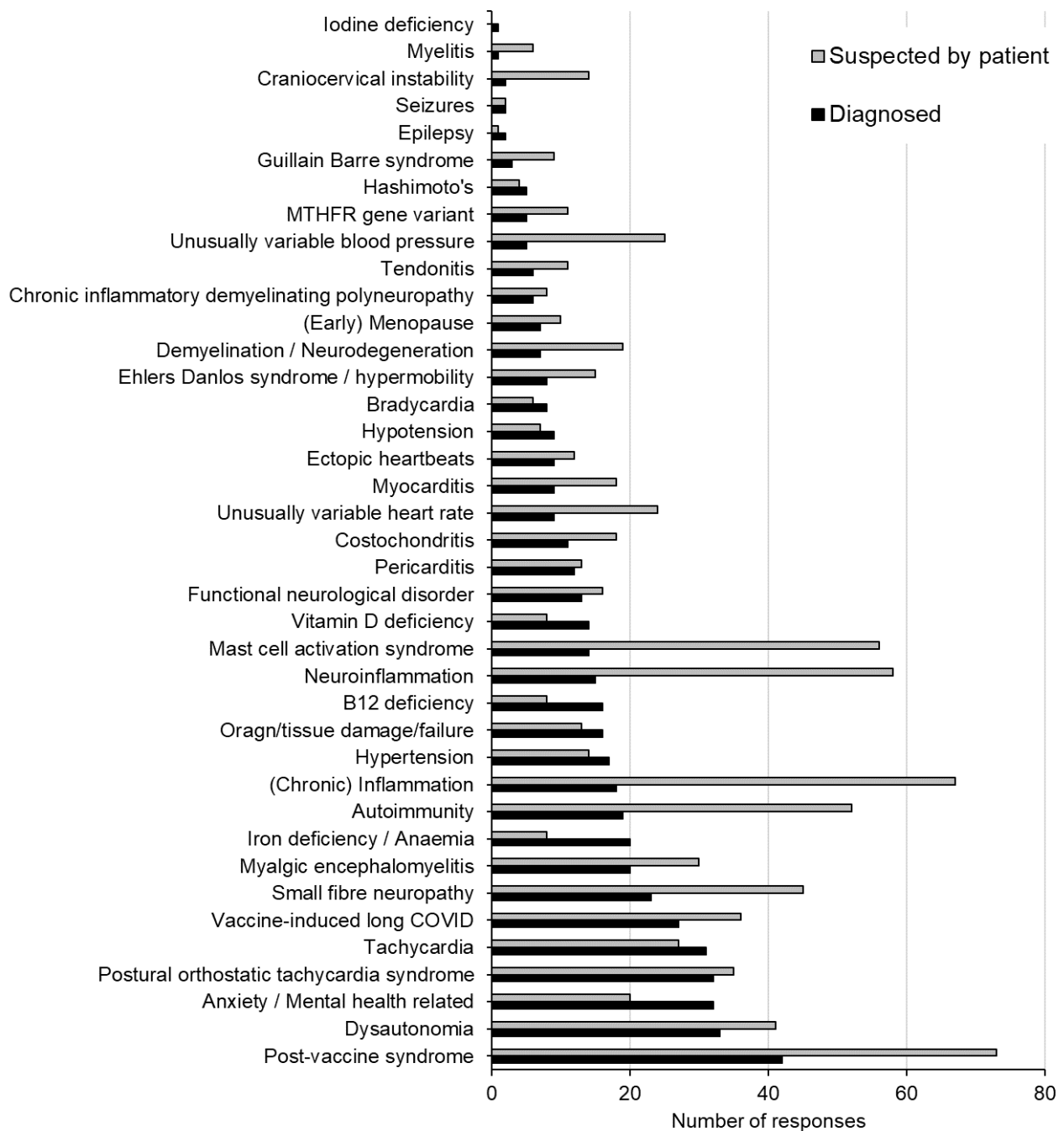


Figure 7. Diagnoses given, and diagnoses suspected by the participant. Abbreviations: MTHFR, methylenetetrahydrofolate reductase

Treatments

We provided 39 pre-specified treatments. Treatments were tried across a range of time frames since the post-vaccine symptoms started (**Supplementary Material Figure S7**). Most commonly tried were: vitamin D (44 %), antihistamines (40 %), and magnesium (33 %); Paxlovid, Goldic, non-steroidal immunosuppressants, intravenous immunoglobulin (IVIG), monoclonal antibodies, hydroxychloroquine, and angiotensin receptor blockers were tried by ≤ 1 % of respondents. Based on treatments that > 20 respondents had tried, mast cell

stabilisers, a low histamine diet, and hydration/electrolytes were most commonly rated as “consistently helpful” (50 %, 50 %, and 44 %, respectively). The worst treatment (i.e. ranked as “consistently made things worse”) was steroids (13 %), whilst common treatments that “consistently did nothing” included ivermectin (30 %), fibrinolytic supplements (e.g. nattokinase) (21 %), and magnesium (21 %) (**Figure 8**).

Unwanted side effects from treatments were relatively uncommon. Of treatments with > 20 responses, those with the highest percentage of “no side effects” were low histamine diet (97 %), zinc (91 %), hydration/electrolytes (91 %), and vitamin D (90 %); whilst highest reports of any (mild, moderate, severe) side effects were from antidepressants (77 %), steroids (69 %), fasting (30 %), and antihistamines (25 %) (**Figure 9**). Participants frequently reported taking more than one treatment at the same time (78 % “yes”, 9 % “sometimes”).

Of all treatments tried, 876 were self-prescribed, 191 were prescribed by a GP/equivalent, and 127 by another medical doctor that we did not specify in other options. Other, less frequent, prescribers included neurologists (n = 57), cardiologists (n = 42), immunologists (n = 20), haematologists (n = 11), nurses (n = 2), other conventional medical practitioners (n = 6), functional doctors (n = 22), homeopaths (n = 6), acupuncturists (n = 2), naturopaths (n = 24) nutritionists (n = 8), other complementary/alternative practitioner (n = 2), and other (n = 8). Treatments were started across a range of time spans from symptom onset (**Supplementary Material Figure S8**).

When comparing treatments between mRNA and vector vaccines, some imbalances were found (**Table 5**). However, most treatments had not been tried by a substantive proportion of the sample, and a considerable proportion responded “not sure / mixed results”, making these results more difficult to interpret.

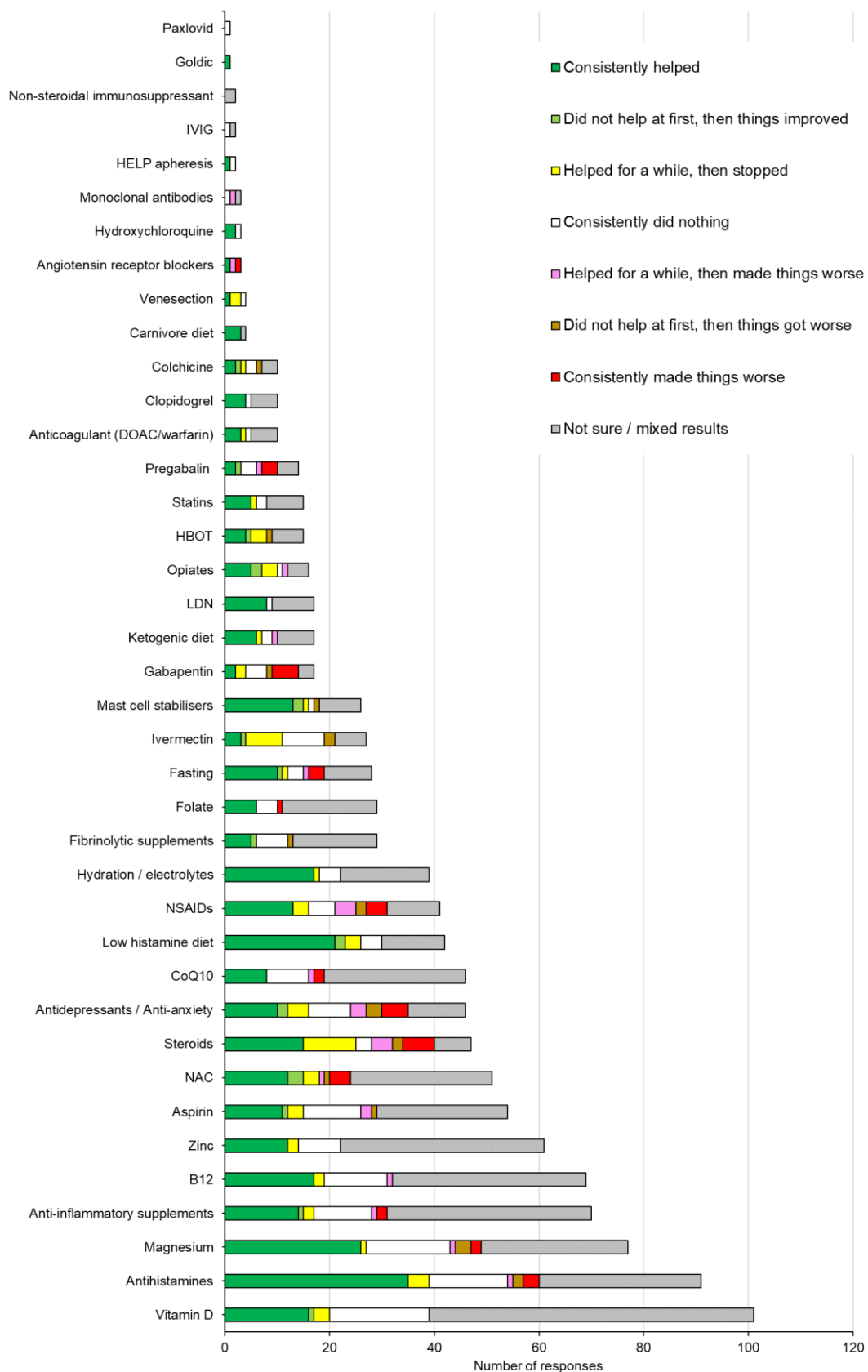


Figure 8. Treatments tried and the impact they had. Abbreviations: CoQ10, coenzyme Q10; DOAC, direct oral anticoagulant; HBOT, hyperbaric oxygen therapy; HELP, heparin induced extracorporeal LDL precipitation; IVIG, Intravenous immunoglobulin; LDN, low dose naltrexone; NAC, N-acetyl cysteine; NSAIDs, non-steroidal anti-inflammatory drugs

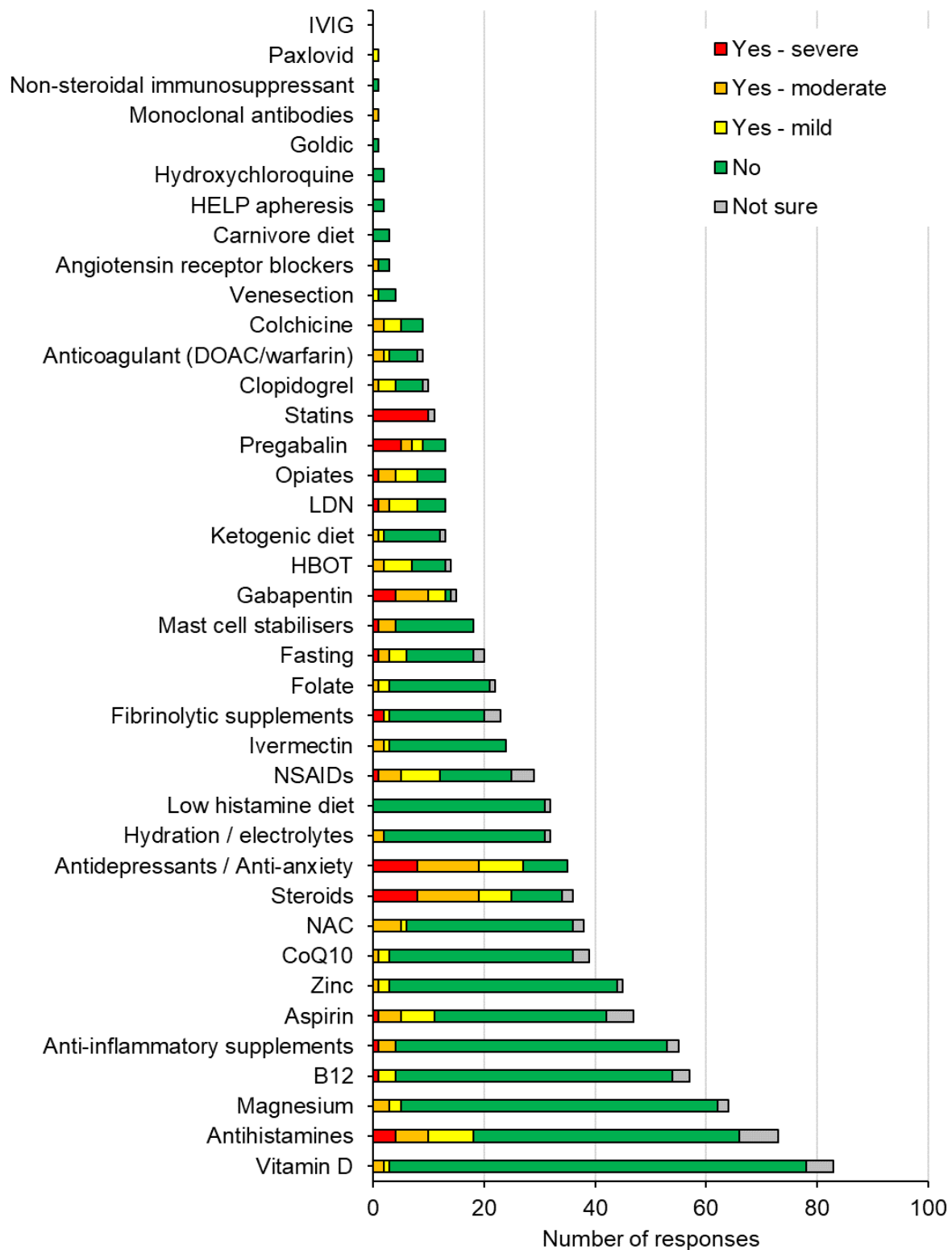


Figure 9. Severity of unwanted side effects experienced for the pre-specified treatments. Abbreviations: CoQ10, coenzyme Q10; DOAC, direct oral anticoagulant; HBOT, hyperbaric oxygen therapy; HELP, heparin induced extracorporeal LDL precipitation; IVIG, Intravenous immunoglobulin; LDN, low dose naltrexone; NAC, N-acetyl cysteine; NSAIDs, non-steroidal anti-inflammatory drugs

Table 5. Treatment imbalances according to vaccine type

Treatment	Vector (n = 86)								p-value
	Helped for a while, then stopped	Consistently helped	Helped for a while, then made things worse	Did not help at first, then things improved	Consistently did nothing	Did not help at first, then things got worse	Consistently made things worse	Not sure / mixed results	
Vitamin D n (%)	3 (8)	8 (21)	-	-	2 (5)	-	-	25 (66)	-
Aspirin n (%)	-	2 (9)	1 (5)	-	2 (9)	-	-	17 (77)	-
Carnivore diet n (%)	-	3 (100)	-	-	-	-	-	-	-
Treatment	mRNA (n = 143)								p-value
	Helped for a while, then stopped	Consistently helped	Helped for a while, then made things worse	Did not help at first, then things improved	Consistently did nothing	Did not help at first, then things got worse	Consistently made things worse	Not sure / mixed results	
Vitamin D n (%)	-	8 (13)	-	1 (2)	17 (27)	-	-	37 (59)	0.013
Aspirin n (%)	3 (9)	9 (28)	1 (3)	1 (3)	9 (28)	1 (3)	-	8 (25)	0.015
Carnivore diet n (%)	-	-	-	-	-	-	-	1 (100)	0.045

Data analysed using χ^2

Cluster analysis

Clustering did not appear to yield useful results with clearly defined subgroups; the Silhouette score ranged from 0.127 to 0.287 for the five clustering models made, and the Dunn index ranged from 0.339 to 0.416, both indicating significant overlap between clusters. We have presented the cluster analyses in the **Supplementary Material (Figure S9a-e and Tables S5a-e; Table S5a** also includes a list of open-ended responses for symptoms, tests, diagnoses, and treatments) for transparency but our interpretation is that these are not useful in identifying clear clusters. Because of this, the regression results are not deemed reliable, though have been reported in the **Supplementary Material (Table S6)**; the tentative relationships identified could be worthy of further exploration.

Participant perception

We asked why participants felt it was difficult to get a diagnosis. Responses predominated around lack of awareness, knowledge, and research (**Supplementary Material Figure S10**). We asked participants to compare their perceptions of conventional medicine *versus* CAM. Overall, participant rated CAM treatment as “excellent” more frequently than conventional medicine ($n = 21$ *versus* $n = 3$, respectively). Ratings changed inversely between the two types of medicine, resulting in conventional medicine being commonly rated as “abysmal” ($n = 62$) compared to CAM ($n = 5$) (**Supplementary Material Figure S11**).

We asked respondents to select whether they agreed with a range of positive, neutral, and negative words describing healthcare from conventional medicine *versus* CAM. Both types of care were rated similarly for positive and neutral words, however, conventional medicine was consistently ranked highly for negative words, whilst CAM tended to get fewer negative word votes (**Supplementary Material Figure S12**).

Discussion

Whilst growing in recognition in the academic literature and among clinicians (Finsterer, 2022a; e.g. Schieffer and Schieffer, 2022; Scholkmann and May, 2023), there are currently no clinical guidelines for what is increasingly recognised as long COVID-like chronic COVID-19 vaccine adverse events. This has left clinicians unable to apply evidence-based medicine, resulting in patients being inadequately treated, likely contributing to prolonged ill-health. This study aimed to characterise long COVID-like chronic COVID-19 vaccine adverse reactions in order to offer insight into potential pathology, and spur further research. Overall, we found respondents had an extremely high burden of symptoms leading to ratings of health being overall poor, in line with another recent survey in this patient population (Krumholz et al., 2023). Test results often came back normal, though, concerningly, 13 % reported not having had any tests. Certain treatments appeared to be more likely to help, such as mast cell targeting treatments and hydration/electrolytes. Participant perception and experience of healthcare was overall poor.

Our cluster analyses did not yield clear subgroups. Previous research in long COVID has identified clusters of symptoms (e.g. Zhang et al., 2023), however, such studies utilised much larger datasets. It is therefore crucial to collect more data on this patient group; we note REACT19 is currently collecting data with a view to reaching > 2000 participants. Despite the lack of clear subgroups, the reported symptoms, test results, and diagnostics do point towards certain pathological processes, which can help guide clinicians, researchers, and patients.

The most common symptoms reported are in line with chronic (more typically infection-associated) illnesses, such as myalgic encephalomyelitis (ME) and POTS. Such illnesses have been reported after non-COVID-19 vaccinations (e.g. Blitshteyn et al., 2018; Brinth et al., 2015), though signals have not been found to indicate an overall increased risk at a population level. However, individuals can still incur adverse reactions, even if population signals are lacking (Deans et al., 2022); indeed, individual cases with biological plausibility can be weighted just as heavily as population signals for determining causality (Stratton et al., 2011). Both our results and those of Krumholz *et al.* (2023) found that symptom onset was typically rapid, commencing within days; this improves confidence in a causal link to a vaccine, though longer onset time is expected with predominant autoimmune presentations (e.g. Guillain-Barre syndrome has a typical onset of up to ~5-6 weeks; Ogunjimi *et al.*, 2023).

Nonetheless, a population signal for POTS-like presentations post-COVID-19 vaccine has recently been reported (Kwan et al., 2022). POTS and dysautonomia were two of the most common diagnoses reported by our respondents, in line with a recent survey in post-vaccine syndrome patients by Krumholz *et al.* (2023). Due to lack of awareness among clinicians, dysautonomia and POTS are frequently missed. We note that anxiety/mental health related diagnoses were as common as dysautonomia in our survey—the symptoms of which can look similar to anxiety, particularly in the face of “normal” test results. In addition, MCAS can present psychiatrically (Weinstock et al., 2023). Thus, it is possible that some of these patients are experiencing organic pathology that is manifesting psychiatrically.

Several participants reported thinking they might have a diagnosis they had not had confirmed. A common comorbidity with POTS is small fibre neuropathy (SFN), which was also commonly reported. However, about twice as many participants thought they may have SFN as had been diagnosed. Similarly, about three times as many participants thought they might have autoimmunity than had actually been diagnosed. Autoimmunity is a recognised

potential consequence from vaccination (Chen et al., 2022; Murphy and Longo, 2022; Nune et al., 2023; Vadalà et al., 2017) but challenges remain for diagnosis, especially for seronegative presentations (Lenti et al., 2022), alongside difficulty accessing appropriate tests. MCAS is under-recognised and often considered myopically (e.g. anaphylaxis) (Afrin et al., 2021) but growing evidence suggests it can manifest systemically without typically allergic-type reactions nor a positive tryptase (Afrin et al., 2021). About four times more participant thought they had MCAS than those who had a diagnosis.

For most test results, the most common answer regarding the result was “not sure”. This may represent cognitive dysfunction and the mental burden of the survey and/or poor communication from healthcare professionals. The latter should be investigated as informed consent cannot be given if a patient does not know their results. After “not sure”, the majority of test results came back “normal”; that patients are clearly significantly unwell suggests that the wrong tests are being conducted, and/or the right tests are not currently available. Normal test results were more common in those reporting symptom onset after a mRNA vaccine, which may pose unique challenges in getting diagnosed in this patient subset.

Tests that were reported to more commonly come back abnormal include: blood pressure, cholesterol, ECG/Holter monitor, D-dimer, white blood cells, ANA, vitamin B12, tilt table test, EBV, and CRP. However, bar blood pressure these came back abnormal in < 20 respondents, likely due to lack of testing for many non-standard tests. Of interest, of those who had research-only tests, results frequently showed abnormalities, such as G-protein coupled receptor autoantibodies, venous oxygen saturation, and fibrinoid microclots. We therefore need urgent validation studies in order that clinicians can find and treat the underlying pathology.

In terms of treatments, it seems participants may have been largely left to treat themselves, considering most common treatments were over-the-counter. Clinicians have a duty to “do no harm”, yet leaving patients without treatment can cause harm. Of treatments that > 20 participants had tried, the most commonly reported “consistently helpful” included MCAS-targeted therapies (e.g. antihistamines), POTS-targeted therapies (e.g. hydration/electrolytes), and anti-inflammatories/immune suppressors (e.g. steroids). Research should investigate the heterogeneity in responses, for example, steroids caused a high rate of side effects and worsened many respondents. As such, caution, monitoring, and adaptability are needed when trying treatments.

Although the clustering showed no clear subgroups, these symptoms, test results, diagnoses, and response to treatments suggest neuroimmune dysfunction may be at the core of a significant proportion of patients with long COVID-like presentations post-vaccine. In addition, both microclots and D-dimer results suggest that thrombotic processes may be contributing to symptoms in some patients. Neuroimmune dysfunction (Carroll et al., 2022; Patterson et al., 2022; Patterson et al., 2022; Safavi et al., 2022), autoimmunity (Nune et al., 2023; Semmler et al., 2023; Talotta and Robertson, 2021), and thrombotic vasculitis (Finsterer, 2022b; Kerr and Carroll, 2023; Turner et al., 2023) are in-line with current published and clinical evidence (Carroll and Deans, 2022; Couzin-Frankel and Vogel, 2022; Schieffer and Schieffer, 2022; Scholkmann and May, 2023; Vogel and Couzin-Frankel, 2023), as well as concordant with what we understand of SARS-CoV-2-induced long COVID (Davis et al., 2023; Kerr and Carroll, 2023; Sapkota and Nune, 2022; Turner et al., 2023) and related illnesses such as ME (Kell and Pretorius, 2022; Patterson et al., 2022; Wirth and Scheibenbogen, 2020).

In addition, viral vector vaccines were found to be uniquely thrombotic, causing VITT. In our survey, those who had a vector vaccine (predominated by AstraZeneca recipients) were more likely to have elevated D-dimer and urea, low platelet and red blood cell count, and abnormal (high or low) haematocrit and white cell counts. In addition, these participants were more likely to suffer certain symptoms, such as vision problems, joint inflammation, tremors, and weakness. This might indicate several things.

Firstly, it should be explored whether there are other variations of VITT that are not immediately life threatening but possess similar clinical characteristics. Testing patients for anti-platelet factor 4 might help identify whether some of them have a currently unrecognised form of VITT, or whether the thrombosis is via another mechanism. Along these lines, whether the adenovirus vector has unique roles in long COVID-like reactions (as with VITT; Greinacher et al., 2022) should also be explored. Secondly, it signals towards the role of coagulopathy in symptoms that are not typically associated with clotting, such as tremors. Indeed, growing evidence points towards post-vaccine coagulopathy in causing vision problems (Finsterer, 2022b), as well as a range of neurological or non-specific symptoms—for example, a case series reported an alleviation in long COVID symptoms after triple anticoagulation therapy (Laubscher et al., 2023). It is also noted that antiphospholipid syndrome, an autoimmune clotting disorder, shares very similar symptoms, and these antibodies may be implicated in vaccine-related complications (Talotta and Robertson, 2021). Thirdly, growing evidence suggests microclots and platelet hyperactivation may be important factors in long COVID pathology (Kell et al., 2022; Kerr and Carroll, 2023; Turner et al., 2023). It is unclear from our results whether vector vaccines cause a particularly high microclot burden, or whether another form of thrombosis is (perhaps simultaneously) occurring. Since fibrinolytic supplements were most often rated as “consistently did nothing”, it may indicate that other forms of coagulopathy are predominating, such as platelet hyperactivation. These ideas should be investigated, including whether there are pathological differences in post-vaccine patients who received vector *versus* mRNA vaccines.

Participant experience

Whilst not the primary aim of the survey, we did ask about participants’ healthcare experience. Krumholz *et al.* (2023) reported on the significant challenges patients face in their day-to-day lives, including feelings of fearfulness and overwhelm. Our findings suggest participants rated their healthcare overwhelmingly as poor, very poor, or abysmal, whilst CAM practitioners were more commonly rated “excellent”, “very good”, or “good”. Interestingly, CAM and conventional medical providers were rated fairly similarly for positive and neutral words (e.g. “empathetic”, “caring”, “listens/believes me”, “works with me as a team”, and “curious”), whilst participants often agreed that negative words (such as “dismissive”, “arrogant”, “closed-minded”, “does not listen/believe me”, and “uninformed”) better captured conventional medicine (but not CAM).

Since CAM is more typically self-funded, this might suggest patients who see CAM practitioners are not necessarily willing to pay extra for greater knowledge, but rather to be believed and bypass medical gaslighting, i.e. it is possible that CAM practitioners are not necessarily considered much better than conventional providers, but are perceived as less bad. This should be further investigated to understand whether the lack of negative attributes is a driving factor towards CAM, as this would provide important lessons regarding improving the healthcare experience (for all patients, not only those with vaccine injury).

In addition, lack of knowledge was most commonly rated as the main perceived reasons for lack of referrals. The General Medical Council (2023) state:

...as a good doctor you will:

- *make the care of your patient your first concern*
- *be competent and keep your professional knowledge and skills up to date*
- *take prompt action if you think patient safety is being compromised*
- *establish and maintain good partnerships with your patients and colleagues*
- *maintain trust in you and the profession by being open, honest and acting with integrity*

Our findings suggest that this guidance is not being upheld from a patient perspective, and this may be contributing to the significant challenges patients reported in Krumholz *et al.* (2023). The qualitative analyses of our open-ended response may provide further insight.

Prompt and thorough investigation of patients suffering from iatrogenic harm not only benefits the patient. In the case of vaccines, it improves vaccine safety monitoring, allows for rapid updates to vaccine inserts, and proffers informed consent to recipients. This is particularly important as unlike other medications, vaccines are given to people currently unaffected by the disease they are targeted at; as such, serious/chronic side effects are less acceptable. For most participants in the survey, many of the symptoms they have experienced chronically were not listed on the insert and still are not listed. Medical professionals therefore have a duty both to their patient, and wider society, to ensure accurate diagnoses are made rapidly. Indeed, we echo comments by Krumholz *et al.* (2023):

Research in this area has the risk of being embroiled in debates about vaccinations. The net benefit of the COVID-19 vaccination program is clear and there are concerns about vaccine hesitancy. But fears of inciting vaccine hesitancy should not impede efforts to research this condition—and make progress for people who are suffering.

Based on these survey results, wider literature, and clinical and patient experience, **Figure 10** gives examples of the types of diagnoses that clinicians should explore with patients presenting with post-vaccination symptoms (with likely relevance to long COVID), with examples of the types of tests that can be useful. Whilst some symptoms can offer a fairly clear clue regarding diagnosis (e.g. postural tachycardia and POTS), it is increasingly apparent that symptoms do not always present “typically” for the underlying pathology (e.g. coagulopathy presenting as neurological symptoms).

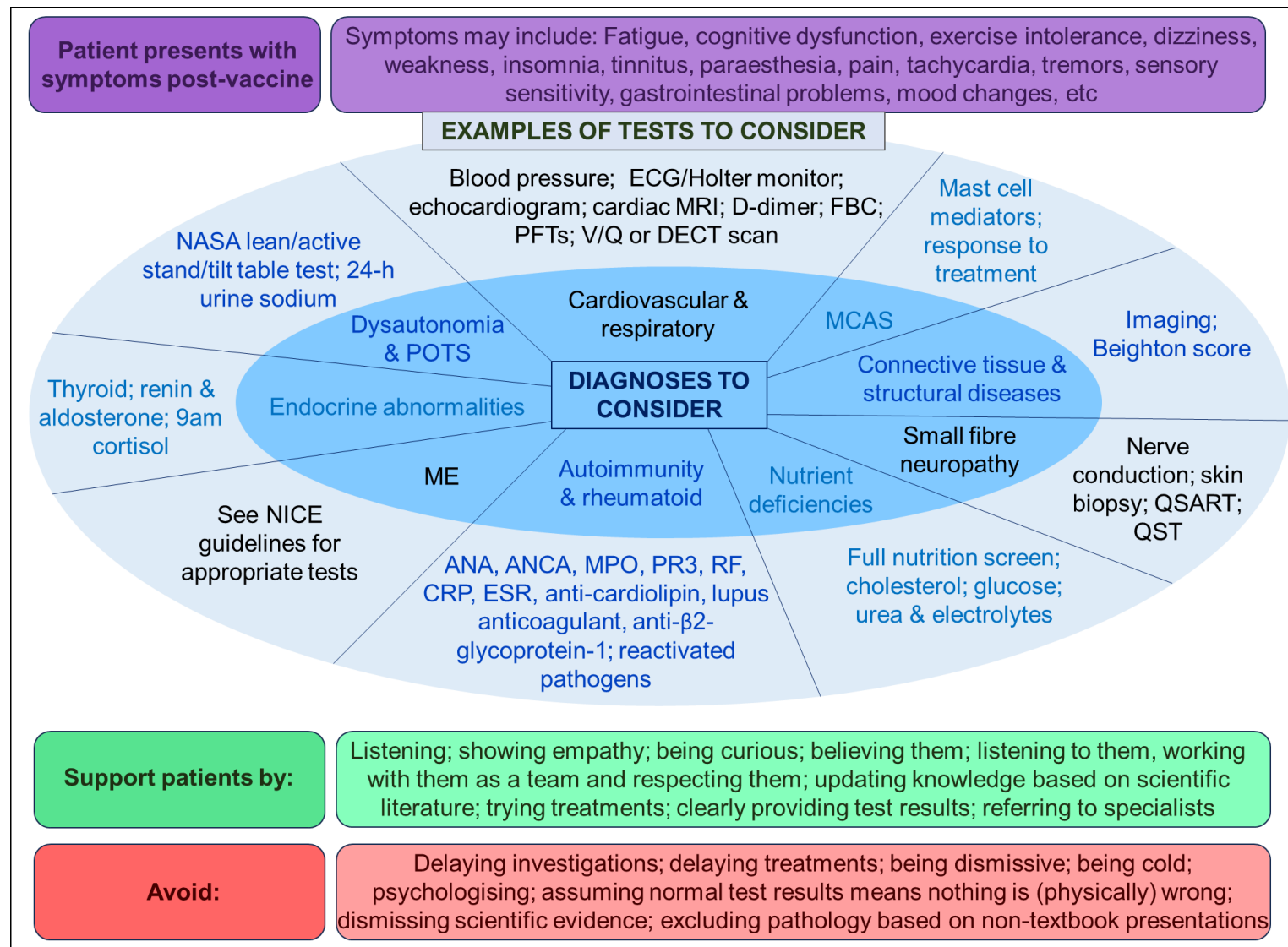


Figure 10. Outline of diagnoses to explore and examples of relevant tests, based both on the current survey, and growing evidence (including clinical experience). Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; ME, myalgic encephalomyelitis; MPO, anti-myeloperoxidase antibody; NICE, National Institute for Health and Care Excellence; PFTs, pulmonary function tests; PR3, anti-proteinase 3 antineutrophil cytoplasmic antibodies; QSART, quantitative sudomotor axon reflex test; QST, quantitative sensory testing; RF, rheumatoid factor

Strengths and limitations

This study did not aim to quantify the prevalence of long COVID-like vaccine reactions, but rather characterise these reactions in those reporting chronic post-vaccine sequelae. As such, we make no claims regarding the safety of the vaccines at a population level based on this survey, whilst recognising that some people have unexpected reactions.

We obviously could not verify the respondents as being vaccine injured. We included a question to ask whether they were part of a support group (and which one, if so) to help reduce the likelihood non-injured would respond. In addition, the survey was quite long which would possibly deter those not fully invested from answering. Equally, the length of the survey was a limiting factor, particularly for more severe patients, so these results are less likely to be generalisable to them, and some participants may have not been able to fully engage with the entire survey (i.e. some answers were incomplete). We hope this research will spur others to investigate the most severe cases who are often unable to participate in research. In addition, our sample was predominantly white, in adults only, and a requirement of the survey was fluency in English, and access to a computer. Research should work towards understanding the diversity of this cohort of patients in order to conduct more representative research. This is particularly important due to added intersectional difficulties faced by some patients when trying to access quality healthcare, and that some patients may have been excluded from our research due to these intersectional disadvantages.

Whilst patients in support groups, to the best of group administrators' abilities, truly believe they are vaccine injured, there is of course the likelihood that some participants' ill-health is due to other factors. Nevertheless, the similarities in experiences, as well as increasing biomedical research, improves our confidence that these reactions could be causal to the vaccine. In our experience, those who had a COVID-19/other infection around the same time of their vaccine are very open to the fact that the vaccine may not be the cause of their symptoms. However, such participants were not excluded from the research, and many infections are asymptomatic; this may introduce bias in a subset of responses.

The survey was conducted in mid-2022, meaning these results are significantly out of date. Since closing the survey, many patients have had new tests, new diagnoses, and different symptom presentations, and patients and academics in the field have a better idea regarding underlying pathophysiology. Equally, in our experience, many patients are still inadequately investigated. Our survey might still prove useful to this group who can compare their earlier symptoms to those in our sample and have some direction regarding the most useful tests to seek and diagnoses/treatments to explore. In addition, since similar vaccine injuries have been reported with non-COVID-19 vaccines (e.g. Afrin et al., 2022; Blitshteyn et al., 2018; Jørgensen et al., 2020), this and other research may offer some direction for these patients, as well as providing insight regarding vaccine safety considerations for any new vaccines that are developed. The urgency of the situation is only increasing, with current patients' health often declining, and other people becoming newly injured. Further, with ongoing unmitigated spread of SARS-CoV-2, obtaining accurate research into "pure" vaccine injury (i.e. without co-infection as a confounder) will become more difficult. As such, we hope these results encourage further investigations in those with post-acute vaccine sequelae.

Nonetheless, our contribution includes a greater proportion of vector vaccine injured participants in comparison to Krumholz *et al.* (2023) who had 88 % of respondents (compared to 62 % in our survey) report injury from a mRNA vaccine, and we had a greater proportion of men and non-binary people (28 and 2 %, respectively, compared to 20 % identifying as male in Krumholz *et al.*). Krumholz *et al.* (2023) excluded those with long

COVID, which we did not do (51 % reporting no known COVID-19 infection prior to vaccination; 2 % reporting infection at a similar time to vaccination; 29 % reporting having long COVID). This makes our results harder to clearly identify vaccine-related symptoms in some respondents, but does better reflect the real-world situation. Finally, our research offers novel contributions, by providing more detail regarding tests, treatments, and diagnoses than the only previous survey we are aware of.

Conclusion

Overall, this survey of n = 230 participants reporting chronic health problems after receiving a COVID-19 vaccine suggests that neuroimmune dysfunction with coagulopathy may be core to the pathophysiology of many patients. This is in line with our current understanding of long COVID and similar illnesses such as ME. However, participant presentation, test results, and response to treatment were heterogeneous. Certain symptoms and tests results were more prevalent after vector vaccines than mRNA vaccines. Research should aim to understand the pathophysiology and treatment of such reactions, and vaccine manufacturers should use this information to develop even safer vaccines. Understanding long COVID-like vaccine reactions may also aid in understanding SARS-CoV-2-induced long COVID by offering insight regarding the role of the spike protein without the confounding effects of viral replication and other viral proteins.

Acknowledgments

The authors would like to thank everyone who completed the survey; we appreciate the significant energy this took and the likely consequences for many from the exertion of doing so. We would also like to thank Dr Kevin Deans for critical input throughout the survey development, analysis, and the manuscript draft; Brian Howard, Catriona Bergman, Christina Wood, and Tracy Coulston for help with survey development and/or pilot testing; and the NHS Grampian Endowment Fund for funds to access the survey platform (<https://www.onlinesurveys.ac.uk/>).

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