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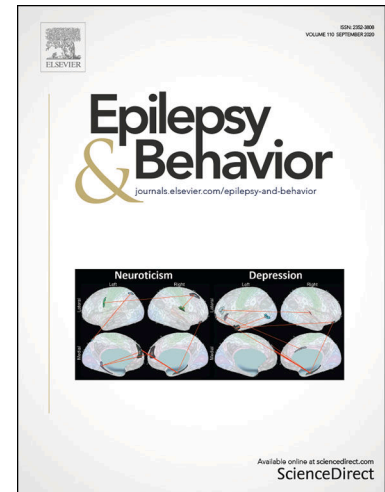
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The impact of SARS-CoV-2 vaccination in Dravet Syndrome: A UK survey

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Highlights

- Caregivers are concerned about SARS-CoV-2 vaccines in people with Dravet syndrome
- SARS-CoV-2 vaccines are safe and well tolerated in people with Dravet syndrome
- SARS-CoV-2 vaccines do not increase seizures in most people with Dravet syndrome

The impact of SARS-CoV-2 vaccination in Dravet Syndrome: A UK survey

Abstract

Background: The COVID-19 pandemic led to the urgent need for accelerated vaccine development. Approved vaccines have proved to be safe and well tolerated across millions of people in the general population. Dravet Syndrome (DS) is a severe, early onset, developmental and epileptic encephalopathy. Vaccination is a precipitating factor for seizures. Whilst there is no evidence that vaccine-precipitated seizures lead to adverse outcomes in people with DS, fear surrounding vaccination can remain for caregivers of people with DS, in some cases resulting in rejection of recommended vaccinations, leaving individuals more vulnerable to the relevant infections. A greater understanding of the safety profile of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in this vulnerable group will help provide guidance for caregivers and clinicians when considering vaccination.

Methods: A cross-sectional survey regarding COVID-19 and SARS-CoV-2 vaccine, in people with DS, was conducted by Dravet Syndrome UK (DSUK). Concomitantly, a review of individuals with DS who had recently received the SARS-CoV-2 vaccine, and who are resident at the Chalfont Centre for Epilepsy (CCE), or attend epilepsy clinics at the National Hospital for Neurology and Neurosurgery (NHNN), was undertaken.

Results: 38 people completed the DSUK survey. 37% of caregivers reported being concerned about someone with DS receiving the SARS-CoV-2 vaccine; with some reporting that they would decline a vaccine when offered. 77% had not received any advice from a health care professional about the SARS-CoV-2 vaccination. 18/38 were eligible for SARS-CoV-2 vaccination, of whom nine had received their first vaccine dose. Combining the results of the DSUK survey and the review of individuals monitored at CCE or NHNN, fifteen people with DS had received their first dose of the SARS-CoV-2 vaccine. 11/15 (73%) reported at least one side effect, the most common being fatigue (6/15; 40%) and fever (6/15; 40%). Three individuals (20%) reported an increase in seizure frequency after the first vaccine dose. No increase in seizure frequency or duration was reported after the second dose.

Conclusion: Overall, these results suggest that SARS-CoV-2 vaccines are safe and well tolerated in individuals with DS, as they are in most people without DS. In most people with DS, SARS-CoV-2 vaccine does not appear to be associated with an increase in the frequency or duration of seizures, even in those who develop fever post-vaccination. Many caregivers are concerned about a person with DS receiving a SARS-CoV-2 vaccine, with some reporting that they would decline a SARS-CoV-2 vaccine when offered. It is crucial that healthcare professionals are proactive in providing accurate information regarding the risks and benefits of vaccination in this population, given the potential for serious outcomes from infection.

Key words: Dravet Syndrome, vaccination, COVID-19, SARS-CoV-2, seizures, side effects

Abbreviations: CCE - Chalfont Centre for Epilepsy; DS – Dravet syndrome; DSUK - Dravet Syndrome UK; PCR - Polymerase chain reaction; SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2

Introduction

The COVID-19 pandemic, which has caused more than 2.5 million deaths worldwide, led to the urgent need for accelerated vaccine development, with the first vaccine entering phase 1 clinical trials in March 2020. At the time of writing, three vaccines have been approved in the United Kingdom, including Pfizer/BioNTech (BNT162b2), Oxford/AstraZeneca (ChAdOx1 nCoV-19) and Moderna (mRNA-1273). These vaccines have proved to be safe and well tolerated across millions of people in the general population [1,2]. However, their safety profile is unknown in specific populations where vaccinations in general can be associated with a higher risk of adverse events.

Dravet Syndrome (DS) is a severe, early-onset, developmental and epileptic encephalopathy, most frequently caused by mutations in *SCN1A*. Onset is typically in the first year of life with prolonged, generalised or hemiclonic febrile seizures. Subsequently, multiple, medically refractory afebrile seizures ensue. Fever sensitivity, as a trigger for seizures, persists into adult life in many individuals with DS [3].

Vaccination may precipitate seizure onset in up to a third of individuals with DS [4–8], and can remain a seizure trigger after seizure onset, even in those whose first seizures were not precipitated by vaccination [5,7]. Multiple vaccine types have been associated with seizure precipitation in DS [5], with the seizure risk dependent on the specific vaccine [9]. Vaccine-precipitated seizures frequently occur without associated fever [5,6,8,9], suggesting that the vaccine-generated immune response may play a role [5].

Importantly, people with DS whose first seizures are precipitated by vaccination show no difference in the age of onset of developmental delay, in the disease trajectory, or in cognitive outcomes, compared with those without vaccine-precipitated seizure onset [6,8,9]. In addition, completion of recommended vaccination schedules is not associated with any difference in cognitive outcome, compared with those who suspended vaccination [8]. Overall, a diagnosis of DS is not a contraindication for further recommended vaccinations [6,10]. Despite this evidence, caution, mistrust and fear surrounding vaccination can still remain for caregivers of people with DS [5,6], in

some cases resulting in rejection of recommended vaccinations [5,8], leaving individuals more vulnerable to the relevant infections.

In a recent survey of individuals with DS, no deaths or severe outcomes were reported in people who had symptoms compatible with COVID-19. However, 40% of symptomatic people required medical attention, and 50% reported an increase in seizure frequency and/or duration, during the period of possible COVID-19 infection [11]. Caregiver concerns surrounding vaccination, and the potential for adverse effects of COVID-19, including an increase in seizures, emphasise the need for further information regarding the safety of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in people with DS. Here we present a survey, undertaken early during the roll-out of vaccination for people with DS, of caregiver concerns, side effects and seizure frequency changes in individuals with DS after SARS-CoV-2 vaccination. In addition, we report on the effect of the SARS-CoV-2 vaccine in six individuals with DS who have been part of an enhanced COVID-19 surveillance programme in a long-term care facility [12], or who attend epilepsy clinics at the National Hospital for Neurology and Neurosurgery (NHNN).

Methods

This work formed part of a service evaluation registered and independently approved by the Clinical Audit and Quality Improvement Subcommittee, Queen Square Division, University College London Hospitals NHS Trust. This approval waives the need for approval by an ethics committee, in accordance with UK legislation and NHS operating procedures.

A cross-sectional survey was conducted by Dravet Syndrome UK (DSUK), an independent, patient advocacy group (Charity Number 1128289). The survey was open for responses between 2nd February 2021 and 1st March 2021. The survey was emailed by DSUK to registered families, who care for at least one child or adult with a confirmed diagnosis of DS, and who had consented to be contacted by email. Families were invited to complete the survey anonymously with the stated purpose of improving clinical understanding of the SARS-CoV-2 vaccination in people with DS in the UK.

Contributors who reported receiving the first SARS-CoV-2 vaccine dose in the initial survey, and who agreed to be contacted for further information, were approached again in June 2021 and invited to provide details regarding the second SARS-CoV-2 vaccine dose. Families were advised that the results would be shared with DSUK's medical advisory board and made public subject to consultation with DSUK's medical advisory board. Families were given details of DSUK's data handling policy and also given a contact email address at DSUK for any questions arising. No personal information is included in this report of the results of the survey.

A review of individuals with DS, who attend clinics at the NHNN, or are resident at the Chalfont Centre for Epilepsy (CCE), a long-term care facility for adults with severe epilepsy and other co-morbidities, was undertaken. All residents at the CCE undergo weekly polymerase chain reaction (PCR) testing for SARS-CoV-2, as part of an enhanced surveillance programme, since 17 April 2020 [12].

Results

Results of DSUK cross-sectional survey

Demographics

A total of 38 responses were returned, representing information from 13 adults (18 years and over) and 25 children (under 18 years) with DS. Their age ranges were: under 5 years (n = 6), 5–11 (n = 7), 12–17 (n = 12), 18–24 (n = 5), 25–34 (n = 4), 35–44 (n = 4). Responses were received from across the UK. Thirty-two individuals were primarily resident at their family home during lockdown, whilst six individuals were primarily living in residential facilities.

Vaccine concerns and advice

13/35 (37%) caregivers reported being “concerned” or “very concerned” about someone with DS receiving the SARS-CoV-2 vaccine; whilst 11/35 (31%) were “unconcerned” or “very unconcerned”. 27/35 (77%) people had not received any advice from a healthcare professional about the SARS-CoV-2 vaccine, of whom 25 had not requested information or advice, and two had asked for advice but had not received any. 7/35 (20%) had received advice about the SARS-CoV-2 vaccine from a healthcare professional, including from their general practitioner, paediatrician, neurologist, DSUK webinar or other healthcare professional. Three individuals did not complete this section of the survey.

Free text responses highlighted that concerns regarding the SARS-CoV-2 vaccine were occasionally associated with previous negative experience with vaccination (Box 1).

Box 1: A selection of comments from caregivers regarding SARS-CoV-2 vaccine concerns

Level of reported concern	Free text comments
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regarding the SARS-CoV-2 vaccine	
“Very concerned”	“Due to previous experience of reaction to vaccination”
“Very concerned”	“The vaccine will be declined if/when offered”
“Very concerned”	“It is quite a leap of faith asking a parent of a Dravet child to get them vaccinated not knowing the potential effects on the condition.”
“Concerned”	“She does not do well with vaccinations. As she has had the virus back in April and had antibodies in October I probably would not take up vaccine offer.”
“Neither concerned or unconcerned”	“I have been anti-vaccines up to now but my son is so vulnerable..., so we were desperate to get the vaccine, to keep him safe.”

Vaccine uptake

At the time of the survey, SARS-CoV-2 vaccine was only available for individuals aged 16 years and over, such that 18/38 survey respondents were eligible for the vaccine. 9/18 (50%) had received the first dose, of whom 2 (22%) had received the Pfizer/BioNTech vaccine, and 7 (78%) the Oxford/AstraZeneca vaccine (Table 1). The remaining nine individuals were waiting to receive their first dose. No one from the eligible group reported declining an offered vaccination. Details regarding the second dose of SARS-CoV-2 vaccine were only available for four individuals, all of whom had received a second dose of the Oxford/AstraZeneca vaccine.

Side effects of SARS-CoV-2 vaccine

All nine (100%) individuals who had received their first dose of a SARS-CoV-2 vaccine reported experiencing at least one side effect, the most common being fatigue (6/9; 67%), fever (5/9; 56%) and pain at the injection site (5/9; 56%). The median number of side effects experienced was three (range 1 – 6) (Table 1). Side effects appeared to be similar in nature across all age groups, and with both vaccine types, although numbers were too small for statistical comparison.

For the four individuals who had received the second dose of the Oxford/AstraZeneca vaccine, two did not experience any side effects, one individual reported pain at the injection site only, and one individual reported pain at the injection site, fatigue, and fever after the second dose. There was no reported increase in seizure frequency or duration after the second SARS-CoV-2 vaccination.

Only one (11%) individual reported an increase in seizure frequency after the first dose SARS-CoV-2 vaccine (Table 1). This individual had been seizure free for 10 years prior to vaccination, and experienced a seizure 11 days after their first dose of the Oxford/AstraZeneca vaccine. This individual also experienced side effects of fever, fatigue and aching after the first vaccination. They did not experience any side effects, including further seizures, after the second vaccine dose.

Side effects of SARS-CoV-2 vaccine in individuals with prior COVID-19

2/9 individuals who received a SARS-CoV-2 vaccine reported previously having symptoms of COVID-19. One individual (aged 25-34) had previous suspected COVID-19 based on clinical symptoms, but was not tested with swab testing or antibody testing. They required input from their GP for management of their COVID-19 symptoms, and antibiotics were given. Subsequently, they received the Oxford/AstraZeneca vaccination. Side effects after the first dose included a sore arm and swelling at the injection site, fatigue, aching, fever as well as chills, diarrhoea, tachycardia and worsening of existing problems with swallowing. All symptoms resolved after five days. There was no change in seizure frequency or duration around the time of the vaccination. The other individual (aged 16 - 17) had previously had symptoms of COVID-19 with a fever and chills, and a positive PCR test for SARS-CoV-2. They did not require medical input for management of their COVID-19 symptoms. They subsequently received the Pfizer/BioNTech vaccination. Side effects after the first dose included a sore arm, fatigue and aching. There was no change in seizure frequency or duration around the time of the vaccination.

COVID-19 symptoms after first dose of SARS-CoV-2 vaccine

No individuals reported experiencing COVID-19 symptoms, or the need for symptomatic COVID-19 testing, in the time period between their first dose SARS-CoV-2 vaccine and completion of the survey, which was an average of 15 days (SD +/- 5.2) after the first dose.

Table 1: First dose SARS-CoV-2 vaccine uptake and side effects by age group in people with DS

	Age range				
	16 – 17 years (N = 5)	18–24 years (N = 5)	25–34 years (N = 4)	35–44 years (N = 4)	All ages (16 – 44 years) (N = 18)
First vaccine dose received (N (%))					
Yes	2 (40%)	3 (60%)	3 (75%)	1 (25%)	9 (50%)
No	3 (60%)	2 (40%)	1 (25%)	3 (75%)	9 (50%)
Vaccine type (N (%))					
Pfizer/BioNTech	2 (100%)	0	0	0	2 (22%)
Oxford/AstraZeneca	0	3 (100%)	3 (100%)	1 (100%)	7 (78%)
Local or systemic reactions after first vaccination (N (%))					
Yes	2 (100%)	3 (100%)	3 (100%)	1 (100%)	9 (100%)
No	0	0	0	0	0
Pain at injection site	1 (50%)	1 (33%)	2 (67%)	1 (100%)	5 (56%)
Fatigue	1 (50%)	2 (37%)	2 (67%)	1 (100%)	6 (67%)
Headache	0	2 (37%)	1 (33%)	0	3 (33%)
Aching	1 (50%)	1 (33%)	2 (67%)	0	4 (44%)
Nausea or vomiting	0	0	0	0	0
Fever	1 (50%)	2 (37%)	2 (67%)	0	5 (56%)
Allergic reaction	0	0	0	0	0
Other	0	0	1 (33%) ^s	0	1 (11%)
Average number of symptoms experienced (median (range))	2 (1-3)	3 (1-4)	4 (1-6)	2	3 (1-6)

Increased seizure frequency					
Yes	0	0	1 (33%)	0	1 (11%)
Increased seizure length					
Yes	0	0	0	0	0
COVID-19 symptoms after SARS-CoV-2 vaccine					
Yes	0	0	0	0	0
No	2 (100%)	3 (100%)	3 (100%)	1 (100%)	9 (100%)

§ - Other symptoms experienced by this individual after the vaccine included diarrhoea, fast heart rate, chills, throat issue-with swallowing, lump at injection site, sneezing

Results of the NHNN and CCE service evaluation

Three individuals with DS who attend outpatient clinics at NHNN, and three individuals who are resident at the CCE, are also reported here to provide more information on SARS-CoV-2 vaccination in DS (Table 2). Five individuals have pathogenic or likely pathogenic variants in *SCN1A*, according to American College of Medical Genetics (ACMG) guidelines. One individual (case six) has a phenotype consistent with DS, but had negative *SCN1A* sequencing and multiplex ligation-dependent probe amplification (MPLA) in 2010, and is currently undergoing whole genome sequencing. All three residents at the CCE have been part of an enhanced surveillance programme, undergoing weekly PCR testing for SARS-CoV-2 since 17 April 2020 [12]. Since the residents' received their first SARS-CoV-2 vaccination, all three individuals have had negative results on weekly SARS-CoV-2 PCR testing.

Case one is in his forties and is resident at the CCE. He has intellectual disability, spastic quadriplegia and scoliosis. He has never had symptoms of COVID-19, and has remained negative on weekly PCR testing for SARS-CoV-2 since April 2020. He received the first dose of the Oxford/AstraZeneca vaccine in January 2021, and the second dose of the Oxford/AstraZeneca vaccine in March 2021. There were no reported side effects, or change in seizure frequency or duration after either vaccination.

Case two is in his thirties and is resident at the CCE. He has intellectual disability and mild kyphosis. He first tested positive for SARS-CoV-2 on surveillance PCR testing in April 2020. He was promptly isolated and carefully monitored at the CCE, as per published protocols [12]. He remained asymptomatic throughout, although subtle clinical manifestations of COVID-19, such as loss of taste or smell, may have gone undetected. There was no change in his frequent seizures. He was de-isolated after two consecutive negative SARS-CoV-2 PCR tests. He continued to have negative SARS-CoV-2 PCR tests on weekly surveillance, until January 2021 when he tested positive for SARS-CoV-2 on PCR testing for a second time. He continued to test positive on nine consecutive SARS-CoV-2 PCR tests over 27 days. He remained asymptomatic throughout, with no change in seizures. He received the first dose of the Oxford/AstraZeneca vaccine in March 2021, and the second dose of Oxford/AstraZeneca vaccine in May 2021. There were no reported side effects, or change in seizure frequency or duration, after either vaccination.

Case three is in his sixties and is resident at the CCE. He has a gastrostomy in situ for supplemental nutrition due to periods of anorexia and weight loss, but still maintains oral intake. He developed fever, cough and drowsiness in April 2020, testing positive for SARS-CoV-2 on PCR testing. He was isolated and subsequently required transfer to an acute medical ward due to hypotension and oxygen desaturation. He did not require non-invasive or invasive ventilation, and was managed supportively for COVID-19 pneumonia. A transient increase in seizure frequency in association with his infection was managed with clobazam. His SARS-CoV-2 PCR tests remained positive over 26 days. He subsequently received the first dose of the Oxford/AstraZeneca vaccine in January 2021. In the 48 hours following the vaccination he developed a fever and an increase in seizure frequency. He was treated with paracetamol and clobazam and his symptoms resolved within 48 hours. He received the second dose of the Oxford/AstraZeneca vaccine in March 2021. There were no reported side effects or change in seizure frequency or duration after the second vaccination.

Case four is in her twenties and attends outpatient clinics at NHNN. She has intellectual disability and scoliosis. She has never had symptoms of COVID-19. She received the first dose of the Pfizer/BioNTech vaccine in February 2021, and the second dose of the Pfizer/BioNTech vaccine in April 2021. There were no reported side effects after the first dose, and only mild drowsiness after the second dose. There was no change in seizure frequency or duration after either vaccination.

Case five is in her fifties. She has intellectual and behavioural difficulties and crouch gait. She was admitted to hospital with symptoms of COVID-19, and tested positive for SARS-CoV-2 on PCR testing, in January 2021. She required supplemental oxygen therapy but did not require non-invasive or invasive ventilation. She subsequently received both doses of the Oxford/AstraZeneca vaccine in February and March 2021. There were no reported side effects or change in seizure frequency or duration after either vaccination.

Case six is in his twenties and attends outpatient clinics at NHNN. He has severe intellectual disability, obsessive-compulsive tendencies, and a crouched gait. He has never had symptoms of COVID-19. He received both doses of the Oxford/AstraZeneca vaccine (precise dates unknown). After the first vaccine dose he was generally unwell, with an increased seizure frequency that lasted for five days. There were no reported adverse effects after the second vaccine.

Table 2: SARS-CoV-2 vaccination side effects in people with DS attending outpatient clinics at NHNN, or who are resident at the CCE

	SARS-CoV-2 infection prior to vaccination	Vaccine type	Side effects after SARS-CoV-2 vaccination – Dose one	Side effects after SARS-CoV-2 vaccination – Dose two
Case 1	Nil	Oxford/AstraZeneca	Nil	Nil
Case 2	Yes	Oxford/AstraZeneca	Nil	Nil
Case	Yes	Oxford/AstraZeneca	Fever, increase in seizure	Nil

3			frequency	
Case 4	Nil	Pfizer/BioNTech	Nil	Mild drowsiness
Case 5	Yes	Oxford/AstraZeneca	Nil	Nil
Case 6	Nil	Oxford/AstraZeneca	Generally unwell, increase in seizure frequency	Nil

Combined results for the DSUK survey and CCE/NHNN service evaluation

Combining the results of the DSUK survey and the NHNN/CEE service evaluation, 11/15 (73%) individuals with DS reported at least one side effect after the first dose of SARS-CoV-2 vaccination. Fatigue (6/15; 40%), fever (6/15; 40%), and pain at the injection site (5/15; 33%) were the most commonly reported symptoms. Overall, 3/15 (20%) of individuals reported an increase in seizure frequency after the first dose of SARS-CoV-2 vaccination. All three received the Oxford/AstraZeneca vaccine. Of the ten individuals in whom second vaccine dose data were available, three (30%) individuals reported experiencing at least one side effect. No increase in seizure frequency or duration was reported after the second dose.

Discussion

This survey reports caregiver concerns, SARS-CoV-2 vaccine reactions, and seizure frequency and duration in relation to administration of the first dose of SARS-CoV-2 vaccine, in a population of people with DS. 38 people responded to the survey, of whom 18 were eligible for the SARS-CoV-2 vaccine (aged 16 and over). Nine people had received their first dose at the time of the survey. Two people received the Pfizer/BioNTech, and seven received the Oxford/AstraZeneca vaccine.

37% of caregivers reported being “concerned” or “very concerned” about someone with DS receiving the SARS-CoV-2 vaccine. This related to negative experiences with previous vaccines, as well as concerns specifically related to the unknown effects of the SARS-CoV-2 vaccine in DS (Box 1). An anti-vaccine perspective was reported from some respondents, although this did not always translate to rejecting the SARS-CoV-2 vaccine (Box 1). As previously highlighted with regards to childhood vaccinations in individuals with DS [5,8], some caregivers reported that they would not take up the offer of a SARS-CoV-2 vaccine (Box 1).

77% of caregivers had received no information from healthcare professionals regarding the SARS-CoV-2 vaccine. It is crucial that healthcare professionals caring for people with DS are proactive in

providing accurate information regarding the risks and benefits of vaccination. This is particularly important in the DS population, where there may be deep-seated fears surrounding vaccination risk.

Combining the results of the DSUK survey and the NHNN/CEE service evaluation, 11/15 (73%) of individuals with DS reported at least one side effect after the first dose of SARS-CoV-2 vaccination and 3/10 (30%) of individuals reported at least one side effect after the second dose of SARS-CoV-2 vaccination. Mild and self-limiting vaccine-associated side effects (also referred to as reactogenicity) in general are not uncommon in the general population with any vaccine type, and include local reactions at the site of injection, such as pain, erythema and swelling, as well as systemic features, including fever, fatigue and headache [13]. These symptoms are not unexpected, and are a consequence of the inflammatory and immune response induced by all vaccine classes [13,14]. They typically occur 1-2 days after vaccination, but can occur later with some vaccine types, such as the live attenuated measles, mumps and rubella vaccine, where mild viraemia, fever, and rarely febrile seizures, can occur 6-11 days after vaccination [14,15].

The most commonly reported side effects in individuals with DS after the first SARS-CoV-2 vaccine dose were fatigue in 6/15 (40%), fever (6/15; 40%), and pain at the injection site (5/15; 33%). The frequency of reactions in the DS population is not dissimilar to those reported from phase 2/3 trials in healthy individuals and those with stable, chronic disease. After the first dose of the Oxford/AstraZeneca vaccine, 88% of individuals, aged 18 – 55 years, reported at least one local, injection-site reaction, with 86% reporting at least one systemic symptom [16]; the most commonly experienced symptoms were tenderness (76%) and pain (61%) at the injection site, fatigue (76%), headache (65%) and muscle ache (53%) [16]. The reactogenicity profile for healthy individuals and those with stable, chronic disease, aged 16 – 55 years, was similar after the first doses of the Pfizer/BioNTech vaccination, with the most common reactions including pain at the injection site seen in 83%, fatigue in 47%, headache in 42% and muscle pain in 21% [17].

Tenderness and pain at the injection site are the most commonly reported reactions in healthy individuals, and those with stable, chronic disease, aged under 55 years, after both the Oxford/AstraZeneca and Pfizer/BioNTech vaccination, experienced by 61 – 83% [16,17]. These symptoms were slightly less frequently reported in the DS population (only 5/15; 33%). However, these, and other pain symptoms, such as headache, are likely to be under recognised in the DS population due to the difficulty in assessing the presence of such features in individuals with cognitive impairment.

Interestingly, fever was common in the DS population, with 6/15 (40%) reporting this after the first vaccination, including 1/3 (33%) who received Pfizer/BioNTech and 5/12 (42%) who received the Oxford/AstraZeneca vaccine. This is markedly different from that reported in phase 2/3 trials, where only 4% and 24% of those receiving the Pfizer/BioNTech and Oxford/AstraZeneca vaccine, respectively, reported fever [16,17]. Importantly, despite fever being one of the most common precipitants for seizures in people with DS, the majority of individuals had no change in seizure frequency (80%), or seizure duration (100%), after the first dose of vaccination, even in the presence of fever. No increase in seizure frequency or duration was reported after the second vaccine dose.

In clinical trials, prophylactic paracetamol administered before, and every 6 h for 24 h after receiving the Oxford/AstraZeneca vaccine significantly reduced pain, feeling feverish, chills, muscle ache, headache, and malaise, but had no significant effect on reduction of fever; there was no compromise in immunogenicity of the vaccine in those who took paracetamol [18]. Prophylactic paracetamol could be used in people with DS to reduce vaccine-associated side effects, although fever may still occur.

One individual who responded to the survey, and two individuals from the CCE/NHNN service evaluation, reported an increase in seizure frequency after the first SARS-CoV-2 vaccination. The individual responding to the survey, experienced one seizure, 11 days after the first dose of the Oxford/AstraZeneca vaccine. This individual had been seizure-free for 10 years prior to this seizure. They also reported experiencing fever, fatigue and aching after the vaccine. It is unclear if this individual was still experiencing these reactive symptoms, including fever, 11 days after the vaccine, at the time that the seizure occurred. It is generally accepted that for a seizure to be considered to be associated with a vaccination, the event should occur within 72 hours of administration of an inactivated vaccine, and between 7 and 14 days after a live-attenuated vaccine [19]. However, this time-frame guidance is less clear for novel vaccine platforms such as viral vector (Oxford/AstraZeneca) and nucleic acid-based vaccines (Moderna and Pfizer/BioNTech). For both the Oxford/AstraZeneca and Pfizer/BioNTech vaccine, local and systemic reactive symptoms peaked within the first 24 hours after vaccination and had largely resolved by day 7 post vaccination [16,17]. It is thus difficult to attribute the seizure to the vaccine, but clearly there had been a long period of seizure freedom beforehand. No seizures occurred in this individual after their second vaccine dose.

Limited information was available regarding side effects to the second dose of the SARS-CoV-2 vaccine. From the information available there appear to be fewer adverse effects seen with the second SARS-CoV-2 vaccine dose compared to the first dose, although we appreciate that the numbers of cases are small.

In a study by [10], it was found that the release of IL-1 and IL-6, two pro-inflammatory cytokines, were observed in controls.

Conclusion

Although the number of survey respondents was small, overall these results suggest that the SARS-CoV-2 vaccines are safe and well tolerated in individuals with DS, as they are in most people without DS. In the majority of people with DS, SARS-CoV-2 vaccine does not appear to be associated with an increase in the frequency or duration of seizures, even in those who develop fever post-vaccination. Prophylactic treatment with paracetamol and a benzodiazepine, if appropriate, may reduce some side effects and any short-term increase in seizures associated with vaccination in a person with DS.

Many caregivers are concerned about a person with DS receiving a SARS-CoV-2 vaccine, with some reporting that they would decline a SARS-CoV-2 vaccine when offered. It is crucial that healthcare professionals caring for people with DS are proactive in providing accurate information regarding the risks and benefits of vaccination in this population, given the potential for serious outcomes from infection.

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Supporting information

The survey template is available in the Supporting Information.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request, subject to regulatory or other requirements.

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Declarations of interest

JHC has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. None of the other authors have declarations of interests to disclose.