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COVID-19 vaccine allergy advice and guidance: The experience of a UK tertiary referral centre

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ABSTRACT

Objective: The objective was to review COVID-19 vaccine allergy advice and guidance requests received and assess the impact of advice outcome on vaccination outcome.

Design: A retrospective analysis of requests for advice and guidance regarding COVID-19 vaccine allergy was completed using an electronic referral system from February 2021 to January 2022.

Participants: A total of 1265 independent patient requests for advice were received from primary care. Full vaccination information was available on 1210 patients who were included in the analysis.

Main outcome measures: We evaluated the specific outcome of request for advice (written advice versus allergy consultation), rate of vaccination, vaccination combinations, and tolerance of vaccination.

Results: Of the 1210 patients included, 959 (79%) were female. Eight hundred and ninety-six (74%) requests were managed with written advice only and of these 675 (75%) patients went on to be vaccinated. Overall, 891 (74%) of the population were vaccinated with 2 or more doses. Two hundred and nineteen patient consultations were undertaken with 109 (50%) prior to the first vaccination. Forty-nine (45%) consultations prior to vaccination were undertaken due to a label of anaphylaxis to vaccination in the past. Vaccination was recommended for all patients, and 78 (72%) of these received a first dose. Eight of these patients (10%) had symptoms within 1 h of vaccine administration.

One hundred and ten (50%) consultations were undertaken for adverse reactions post COVID-19 vaccination, with 84 (76%) concerning immediate symptoms. Thirty patients (27%) who had a consultation had had adrenaline administered post vaccination. One patient had biopsy confirmed Stevens Johnson Syndrome and was referred to Dermatology. All others due for further doses (107 patients) were recommended to have subsequent doses with 49 (45%) offered the same vaccine. Eighty-nine patients had a vaccine administered post adverse reaction and 79 (88%) tolerated the dose.

Skin testing and challenge to polyethylene glycol were negative in the 8 patients tested.

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Conclusions: Over 1000 requests for advice and guidance were received during the review period, managed mainly with written advice. The overwhelming majority of requests for advice and consultations were for females, with equal distribution both pre- and post-COVID-19 vaccine administration. Vaccination was recommended in all but 1 patient (with biopsy confirmed Stevens Johnson Syndrome). Polyethylene glycol allergy was not confirmed in any patient, nor did any patient have confirmed anaphylaxis when the vaccine was administered under our supervision, suggesting that type 1 mediated hypersensitivity is uncommon even in this "high risk" population.

Keywords: COVID-19, Vaccine, Drug hypersensitivity, Allergy, Polyethylene glycol

INTRODUCTION

The United Kingdom has undertaken a successful vaccination campaign against SARS-CoV-2 with over 49 million people of a population of 65 million having at least 2 doses at the time of writing.[1] Five vaccines are now approved in the United Kingdom, produced by Pfizer/BioNTech (Pfizer), Oxford/AstraZeneca (AZ), Moderna, Janssen, and Novavax. The latter 2 were not available in the United Kingdom during the study period.

The initial roll-out period was complicated by reports of immediate reactions to Pfizer in 2 people with a history of unrelated allergic disease and possession of adrenaline autoinjectors at the time of vaccination.[2] This prompted a swift and broad restriction by the Medicines and Healthcare products Regulatory Agency (MRHA) on vaccination with Pfizer, limiting access in patients with a history of drug-related, vaccine-related, food-related, or unexplained anaphylaxis.[2,3] The inclusion of high molecular weight polyethylene glycol (PEG) in both Pfizer and Moderna vaccines raised concerns about the contribution of PEG allergy to adverse reactions.

Although formal guidelines were updated on December 31, 2020 following further observational data suggesting safety,[3] the legacy of such decisions was clear in the volume of referrals to allergy teams from primary care providers, often prompted by patient concern.

Here we present the results from approximately 12 months of operation of a COVID-19 vaccine allergy service established to manage the requests for advice from primary care physicians. Our service covers an area with approximately 1 million residents and 80 General Practitioner (GP) practices.[4]

METHODS

All patients referred to our adult allergy service through the electronic Referral Service (eRS) for COVID-19 vaccine allergy advice and guidance (A&G) from February 25, 2021 to January 12, 2022 were included in the analysis. Duplicates or multiple requests for the same patient and vaccine dose were removed. Potential outcomes of A&G were as follows: electronic communication of advice through the eRS platform (referred herein as written advice), request for further information, or telephone consultation. The option of administration in a hospital setting without prior consultation was added in June 2021.

The outcome of A&G was determined from a manual list generated at the time of response and eRS was interrogated where required. Consultation data were collected at the time of consultation in a spreadsheet and clinic letters were reviewed where required. Vaccination dates and product information were obtained from the NHS Spine record.

At the time of data analysis, most UK adults were eligible for 2 primary doses and a "booster" dose. In individuals who are immunosuppressed or have an immune deficiency, three primary doses and a fourth "booster" dose was recommended. A patient yet to have completed this regimen was considered "eligible" for further doses.

The advice offered was based on guidelines published in the Green Book (UK Government

publication containing information on immunisation) Chapter 14a,[3] and British Society of Allergy and Clinical Immunology (BSACI) guidelines.[5] Tolerance of a dose was defined as not requiring further specialist allergy advice after administration or symptoms for which no investigation or change in management was required. A reaction was considered immediate if it occurred within 2 h of vaccination as defined by the Green Book. Delayed reactions were those beginning after this time. Cutaneous reactions were those involving skin symptoms only. Systemic reactions were those occurring at a distant site of the body to vaccine administration and involving symptoms other than cutaneous. Peripheral angioedema (for example periorbital) was considered cutaneous and airway angioedema (for example tongue) was considered systemic.

The PEG skin testing protocol used included: Movicol liquid (105 mg/mL macrogol 3350: 1/100, 1/10, neat), Methylprednisolone acetate (40 mg/L), Methylprednisolone succinate (40 mg/L), mRNA vaccine (neat).[6] Intradermal testing was undertaken for Methylprednisolone acetate (0.4 mg/L, 4 mg/L), Methylprednisolone succinate (0.4 mg/L, 4 mg/L),[6] mRNA vaccine (1/1000, 1/100).

RESULTS

Advice and guidance results

Between February 25, 2021 and January 12, 2022 advice was sought for 1265 patients. Advice outcome was available for 1212 patients and full vaccination data were available on 1210 patients.

Nine hundred and fifty-nine patients in whom advice was sought were female (79%) and the mean age was 49 years (range 17–95). Eight hundred and ninety-six requests (74%) were managed with written advice only, whereas 263 (22%) were recommended to have a telephone consultation and 41 (3%) hospital vaccination without consultation. In 10 cases (1%) further information was requested but never received. Table 1 summarises advice and guidance and vaccination outcomes.

Five hundred and eighty-nine requests (49%) were for patients prior to any COVID19 vaccination dose, 456 (38%) prior to their second dose, 152 (13%) prior to their booster or third dose, and 13 (1%) after their third dose. Four hundred patients (68%) in whom advice was sought prior to their first dose had a dose administered following advice being given, 378 (83%) had their second dose after advice was given, 117 (76%) had their third dose after advice given and 1 (8%) had a fourth dose after advice sought. The latter is likely to

	n = 1210	
Female	959	79%
Mean age in years, (range)	49	(17–95)
Timing of advice		
Pre-dose 1	589	49%
Pre-dose 2	456	38%
Pre-dose 3	152	13%
Pre-dose 4	13	1%
Advice outcome		
Written advice	896	74%
Consultation	263	22%
Hospital vaccination	41	3%
Further information	10	1%
Vaccine outcome		
Vaccine administered post:		
Any advice	896	74%
Written advice (n = 896)	675	75%
Consultation (n = 263)	181	69%
Hospital vaccination (n = 41)	35	85%
Further information (n = 10)	5	50%
Overall outcome		
No dose administered	189	16%
One dose	130	11%
Two doses	338	28%
Three dose	544	45%
Four doses	9	1%

Table 1. Summary of overall A&G outcome

reflect guidelines that only a small number of patients were eligible for four doses at the time data was collected.

When comparing vaccination outcome with the advice outcome, 675 (75%) patients had a dose of vaccine after written advice was provided, 181 (69%) of those in whom consultation was recommended, 35 (85%) of those who were allocated to hospital vaccination and only 5 (50%) of those in whom further information was requested but not received. The vaccination rate increased in the consultation category when only those who attended an outpatient virtual or in person consultation were considered (77%).

For the overall population captured, 189 patients (16%) remained unvaccinated at the time of writing, 130 (11%) had 1 dose, 338 (28%) 2 doses, 544 (45%) 3 doses, and 9 (<1%) 4 doses administered. Approximately 74% of the overall population studied had 2 or more doses of vaccine, compared with the population data of 86% at the time of writing.[1] Vaccination combinations for the first 2 doses are shown in Supplementary Table 1.

Consultation results

A telephone consultation was recommended for 263 patients, with a total of 219 (83%) being completed. One hundred and nine consultations (50%) were performed prior to any COVID-19 vaccine doses. The male: female ratio was 1:9 with an average age of 49 years (range 20–82).

Consultation on patients prior to 1st COVID-19 vaccine (109 patients)

The indication for consultation aligned with the Green Book guidelines at the time of referral in 73 (67%) patients (Table 2). Some patients fulfilled more than 1 criteria. In those who did not meet the criteria for referral, most were for adverse reactions to vaccines or medications that were not suggestive of type 1 hypersensitivity. Thirty-two patients (29%) had access to an adrenaline autoinjector prior to consultation and 42 (39%) had comorbid asthma. History taking suggested oral or parenteral tolerance of high molecular weight polyethylene glycol in 44 patients (40%) and polysorbate 80 in 30 (28%).

	Referral (n = 109)	
Female	98	90%
Age (mean in years, range)	52	20–82
Green book Indication		
Anaphylaxis to vaccine	47	43%
Anaphylaxis to an injectable likely to contain PEG	13	12%
Anaphylaxis to multiple medications from different classes	12	11%
Idiopathic anaphylaxis	10	9%
Confirmed mast cell disorder	2	2%
Other indication		
Non-allergic reaction to vaccine	13	12%
Non-allergic drug reaction	6	6%
Urticaria and angioedema	5	5%
Anaphylaxis to single medication	3	3%
Sulphite sensitivity	2	2%
NSAID hypersensitivity	1	1%
Reaction to radiocontrast agent	1	1%
Food allergy[a]	1	1%
Vaccine non responder	1	1%
Chemical reaction	1	1%
Anxiety	1	1%
Self-reported MCAS	1	1%
Comorbid		
Adrenaline autoinjector prescription	32	29%
Asthma	42	39%
Allergic rhinitis	23	21%
Food allergy	17	16%
Chronic spontaneous urticaria	15	14%
Venom allergy	6	6%

Table 2. Indications for consultation prior to vaccination [a]*Primary indication for referral rather than comorbid condition. AR = allergic rhinitis, MCAS = mast cell activation syndrome, NSAID = non-steroidal anti-inflammatory, PEG = polyethylene glycol.*

Vaccination was recommended in all patients. Any available vaccine was recommended in 51 patients (47%) and an mRNA vaccine in 48 patients (44%). Twenty-six patients (24%) were asked to take antihistamines pre-vaccination. Hospital vaccination was suggested in 72 cases (66%) with 1 patient offered skin testing prior (see below).

At the time of writing, 78 (72%) of these patients had had their first dose of COVID-19 vaccine; and of these, Pfizer was administered in 56 (72%), AZ in 18 (23%) and Moderna in 4 (5%). Eight patients (10%) reacted on administration of their first COVID-19 vaccine during the observation period and all but 1 have since had further doses administered (Supplementary Table 2).

Post-vaccination consultation (110 patients)

One hundred and ten consultations were undertaken for adverse reactions post vaccination, with 98 after dose 1 (89%), 10 after dose 2 (9%), and 2 after dose 3 (2%) (Table 3). Eighty-four adverse events prompting consultation (76%) were immediate with 38 (45%) associated with AZ and 45 (54%) with Pfizer. However more delayed reaction consultations were associated with AZ than Pfizer (82% compared to 6%). Most immediate reactions were systemic alone (50%), whereas most delayed reactions were cutaneous alone (53%). Thirty-eight patients (35%) consulted had assessment by paramedics and 39 (35%) presented to hospital. Adrenaline was administered in 30 patients (27%) including 2 patients with delayed symptoms post vaccination. Of the delayed onset symptoms, 1 patient used her own adrenaline autoinjector for angioedema and another had adrenaline administered for urticaria and wheeze occurring more than 24 h post vaccination. This patient experienced ongoing chest pain, lymphadenopathy, unexplained fevers, weight loss, and urticarial vasculitis, and required immunosuppression for symptom control.

In terms of excipient tolerance, 41 patients (44%) with either immediate or immediate and delayed symptoms demonstrated subsequent tolerance to oral or parenteral high molecular weight PEG and 15 (16%) to polysorbate 80.

Vaccination was recommended in all except 1 patient, who experienced biopsy confirmed Stevens Johnson Syndrome temporally associated with AZ vaccination and lamotrigine initiation. The latter was considered the most likely culprit. The patient was referred to a centre with experience in evaluating severe cutaneous adverse reactions. A further 2 patients were not due further doses at the time of consultation; hence, 107 patients were recommended and eligible for a subsequent dose. Seventy-seven patients (72%) were offered hospital-based vaccination. The same vaccine was suggested in 49 patients (46%). Eighty-nine patients (83%) had a subsequent dose administered and 10 patients (11%) had a reaction documented (Supplementary Table 3). Table 4 outlines the vaccine combinations administered when considering the 98 patients who were referred post dose 1.

Skin testing

Skin testing was offered in 10 patients with adverse reaction to a dose of mRNA COVID-19 vaccine and 1 patient prior to any COVID-19 vaccine doses. Three declined evaluation and vaccination. Of the 8 patients who underwent skin testing (Supplementary Table 4), 2 were vaccinated with a non-mRNA vaccination under supervision prior to testing due to patient preference. Both subsequently underwent and tolerated PEG protocol skin testing with Movicol challenge and have been offered mRNA vaccination for their booster dose under supervision, pending at the time of writing. Four patients did not show evidence of sensitisation to PEG or index mRNA vaccine and were vaccinated without complication under supervision. One patient had negative skin testing but experienced flushing, erythema, lightheadedness, and felt unwell with normal observations post her second dose. She subsequently received her booster dose of the same vaccine under supervision with similar symptoms. No dynamic change in her mast cell tryptase was noted on either occasion.

Only 1 patient demonstrated skin test reactivity. A 35-year-old female with acute generalised urticaria post Pfizer was positive to this vaccine intradermally (1/1000 and 1/100 dilution). She did not show evidence of sensitisation to PEG and tolerated a Movicol challenge. In agreement with the patient, she was administered AZ vaccine uneventfully.

	Immediate		Delayed		Both		Overall	
	N = 84		N = 17		N = 9		110	
Female (%)	75	89%	16	94.1%	9	100.0%	100	90.9%
Age	45	(22–78)	55	(27–79)	44	(36–52)	46	(22–79)
Comorbid conditions								
Adrenaline autoinjector prescription	18	21%	4	24%	2	22%	24	22%
Asthma	33	39%	6	35%	5	56%	44	40%
Allergic rhinitis	18	21%	2	12%	3	33%	23	21%
Food allergy	15	18%	3	18%	2	22%	20	18%
Venom allergy	3	4%	2	12%	1	11%	6	5%
Chronic spontaneous urticaria	6	7%	1	6%	0	0%	7	6%
Vaccine details								
Dose 1	74	88%	15	88%	9	100%	98	89%
Dose 2	9	11%	1	6%	0	0%	10	9%
Dose 3	1	1%	1	6%	0	0%	2	2%
AZ	39	46%	14	82%	6	67%	59	54%
Pfizer	44	52%	1	6%	3	33%	48	44%
Moderna	1	1%	2	12%	0	0%	3	3%
Clinical features								
Cutaneous	13	15%	9	53%	1	11%	23	21%
Systemic	42	50%	2	12%	3	33%	47	43%
Both	29	35%	6	35%	5	56%	40	36%
Management								
Ambulance	28	33%	5	29%	5	56%	38	35%
IM Adrenaline (1 dose)	19	23%	1	6%	2	22%	22	20%
IM Adrenaline (2 doses)	5	6%	1	6%	0	0%	6	5%
IM Adrenaline (>2 doses)	2	2%	0	0%	0	0%	2	2%
Hospital presentation	29	35%	5	29%	5	56%	39	35%
Evidence of tolerance								
Tolerance HMW PEG	37	44%	3	18%	4	44%	44	40%
Tolerance PS80	13	15%	0	0%	2	22%	15	14%

(continued)

	Immediate		Delayed		Both		Overall	
	N = 84		N = 17		N = 9		110	
Recommendation								
Vaccination due/recommended	N = 83		N = 15		N = 9		N = 107	
Skin testing	10	12%	0	0%	0	0%	10	9%
Same vaccine	41	49%	7	47%	1	11%	49	46%
H1 Antihistamine	50	60%	12	80%	6	67%	68	64%
Hospital administration	68	82%	0	0%	9	100%	77	72%

Table 3. (Continued) Characteristics of patients who underwent allergy consultation for adverse reactions to COVID vaccination *HMW PEG= High molecular weight polyethylene glycol, IM = intramuscular, PS80 = polysorbate 80.*

Combination	Immediate		Delayed		Both		Overall		Tolerated	
	N = 74		N = 15		N = 9		N = 98			
AZ + AZ	6	8%	4	27%	0	0.0%	10	10%	10	100%
AZ + Pfizer	27	36%	7	47%	4	44%	38	39%	32	84%
AZ + none	2	3%	2	13%	2	22%	6	6%		
Pfizer + Pfizer	17	23%	0	0%	1	11%	18	18%	16	89%
Pfizer + AZ	14	19%	0	0%	2	22%	16	16%	14	88%
Pfizer + none	7	9%	1	7%	0	0%	8	8%		
Moderna + Moderna	1	1%	0	0%	0	0%	1	1%	1	100%
Moderna + none	0	0%	1	7%	0	0%	1	1%		

Table 4. Vaccination outcomes in patients referred prior to their second COVID19 vaccine dose

DISCUSSION

During the 11 months of operation of our COVID-19 vaccine allergy service a very large volume of requests for A&G were received. Other than the scale of the vaccine roll out, other factors played a role in this. There appeared to be lack of referrer awareness of the relevant guidance (eg, the Green Book) and several patients were referred for consultation even after written advice had been provided. These included many patients with self-reported drug allergies but with histories inconsistent with type 1 hypersensitivity. This highlights the importance of appropriate labelling of adverse drug reactions at the time of the adverse event, and the ongoing work needed to improve drug allergy history taking. The importance of this was emphasised in the recent parliamentary report into the National Allergy Crisis.

Despite such high numbers of eRS requests, we recommended vaccination in all patients referred prior to COVID-19 vaccine administration and skin testing only in 1 in this category. Similarly, we recommended vaccination in all but 1 patient for which advice was sought after an adverse reaction to a dose.

A very clear contributor to requests for advice was the inclusion of high molecular weight PEG in both mRNA vaccines approved in the United Kingdom. Literature around PEG allergies is available but remains complex. Questions remain

regarding tolerance of PEG of differing molecular weights, or in different forms such as in capsule coating. The use of skin testing in the diagnosis of PEG allergy has been well described[7-9] but translating skin reactivity at different molecular weights into clinical reactivity is not straightforward. The BSACI outline for allergy specialists suggests skin testing using all available COVID-19 vaccines and excipients in certain adverse reactions.[10] Pitlick et al showed tolerance of mRNA vaccination post adverse event in 15 patients, with all participants undergoing PEG skin testing prior.[11] It has, however, since been hypothesised that most reactions to mRNA vaccines are not mediated by specific IgE targeting PEG, hence limiting the utility of PEG testing.[12,13] The lack of clear benefit on the use of skin testing is reflected in the International Consensus on the evaluation and management of reactions to SARS-CoV-2 vaccines which does not recommend skin testing.[14] The decision to offer skin testing to a few patients through our service was only made after clear discussion with the patient around the limitations of the testing. No patients were given a new diagnosis of a PEG allergy and skin testing changed the recommendations in only one patient. The single patient with positive intradermal testing (IDT) to Pfizer was evaluated very early in the vaccine roll out and may not have been offered skin testing with increasing experience (globally and within our own team) had she been referred later.

It has been suggested that offering a graded dosing strategy may increase vaccination uptake in patients who would otherwise not consent to vaccination.[15,16] Although an option, no evidence to date demonstrates that this approach is safer than single dosing. Our data add to the body of evidence that single dosing strategy is well tolerated. Importantly, no patients vaccinated under our supervision experienced anaphylaxis. A single patient required transfer to the emergency department for further evaluation, subsequently diagnosed with dysfunctional breathing. This suggests that even in a population considered to be "high-risk", life threatening adverse events are rare.

Many patients referred to our service were recommended to have an alternative vaccine. Factors prompting this deviation from recommendations included patient preference. Even prior to evidence supporting the efficacy and safety of heterologous vaccination,[17-20] we hypothesised that mixing vaccines would produce a better immune response than a single dose of the vaccine and hence prioritised full vaccination of patients over ensuring the same vaccine was administered. Although still not part of available allergy guidelines evidently heterologous vaccination is a viable option for patients with a previous suspected reaction to a COVID-19 vaccine. Our practice changed somewhat when restrictions on AZ administration in people <40 years were introduced, and when literature was published on the safety of mRNA vaccines after an adverse reaction to the first dose.[11] This resulted in more people having the same dose administered if their first dose was Pfizer, or an alternative administered if the first was AZ was given initially.

An interesting finding is the high proportion of advice sought and consultations undertaken in females. Several publications have shown that there is a female preponderance of reported adverse drug reactions.[21-23] The odds ratio of female sex and documented anaphylaxis on electronic health records was determined to be 2.2 in 1 study.[24] Several hypotheses have been proposed, including that women report adverse reactions more than men.

An unexpected positive aspect of the rollout of the COVID-19 vaccine A&G service was that it prompted referral of some patients who may have not otherwise accessed our service. Examples include a patient who was diagnosed with wheat dependent exercise induced anaphylaxis, and another who was diagnosed with hereditary angioedema leading to potentially lifesaving treatment.

There are certain limitations to this study. It was undertaken as a clinical service review and hence only specific outcomes were evaluated. Also, any advice that was not sought through eRS was not captured, but this only comprises a very small percent of the total requests. Furthermore, the category "advice given" includes cases in which we may defer to other practitioners (for example cardiologists regarding myocarditis or neurologists regarding Bell's Palsy). The inter-clinician variability

was not explored thoroughly, nor were the differences in advice given over time, considering the 21 updates to the Green Book Chapter 14a that have been made at the time of writing. For example, advice given prior to April 7, 2021, when recommendations on restricting AZ due to concerns about clot risk, was not compared with advice after this time.

CONCLUSION

In the period of February 25, 2021 to January 12, 2022, advice was sought on 1210 patients regarding COVID-19 vaccination, the overwhelming majority of these were in women. Most of the requests were managed with written advice alone, without large differences in the proportion of people vaccinated compared to those who had formal consultation. No patient was diagnosed with a PEG allergy and most patients tolerated COVID-19 vaccination. The impact of a label of a drug allergy in future prescribing practices was highlighted by this mass vaccination program. Improved allergy literacy in the general and referrer population is expected to improve vaccine uptake in similar situations in the future.

Abbreviations

A&G, Advice and guidance; AZ, AstraZeneca; BSACI, British Society for Allergy & Clinical Immunology; COVID19, Coronavirus 2 (SARS-CoV-2); eRS, Electronic referral system; GP, General practitioner; HMW PEG, High molecular weight polyethylene glycol; IM, Intramuscular; MCAS, Mast cell activation syndrome; MRHA, Medicines and Healthcare products Regulatory Agency; mRNA, messenger ribonucleic acid; NSAID, Non-steroidal anti-inflammatory drugs; PEG, Polyethylene glycol; Pfizer, Pfizer/Biontech COVID19 vaccine; PS80, Polysorbate 80

Ethics approval

This was approved as a Clinical Effectiveness Project by the Quality Governance Team at North Bristol Trust (CE8273).

CONTRIBUTORSHIP STATEMENT

FM conceived the evaluation project, designed data collection tools, collected data, analysed data, drafted, and revised paper.

NT, AG, PB and SLJ revised data collection tool and paper.

MG supervised evaluation project, revised data collection tool and paper.

Declaration of Competing interest

All authors declare that we have no conflicts of interest pertinent to this paper.

Consent

All authors consent to publication of this manuscript.

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Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Appendix A. Supplementary data

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