Letter Identification of persons who may respond severely to a hospital-administered Covid-19 vaccine: lessons learned in the Netherlands during the COVID-19 pandemic.

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Letter

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Identification of persons who may respond severely to a hospital-administered Covid-19 vaccine: lessons learned in the Netherlands during the COVID-19 pandemic

INTRODUCTION

Mass vaccination was the main strategy to contain the COVID-19 pandemic. Very early in the vaccination campaign, hypersensitivity reactions were reported, (Ahmadi et al, Chu et al). Adverse reactions occurring between a few minutes, hours or few days after COVID-19 vaccination are quite common with some of these reactions resembling symptoms that are seen in allergic reactions, like urticarial rash, angioedema, shortness of breath, wheezing, nausea, and hypotension (Jaggers et al, Abbaspour et al). Also, during the pandemic, some persons were not vaccinated out of precaution due to a possible or confirmed allergy to one of the excipients of the COVID-19 vaccine like polysorbate 80 or polyethylene glycol (PEG) Krantz et al).

In the Netherlands, the National Institute for Public Health and the Environment (RIVM) published vaccination guidelines that are followed up by the Municipal Health Service (GGD) that was in charge of the Covid-19 vaccination campaign. Since it became known that many persons with a previous response to a COVID-19 vaccination could safely receive a second dose, persons were referred to the allergy departments. In this study the aim was to identify persons at increased risk of reacting severely to a COVID-19 vaccination. If that is possible, more patients can be vaccinated outside the hospital and there is less need to refer to allergy departments in future.

METHOD

Data were collected from persons that were referred because they were considered at increased risk of reacting adversely to the COVID-19 vaccine to the allergy departments in 5 referral hospitals between January 2021 and September 2022 .

Adverse reactions on a previous COVID-19 vaccination were rated into two categories: Moderate to severe manifested with generalized urticaria/erythema , observed angioedema , hypotension or stridor/decrease of oxygen saturation. Mild reactions manifested with subjective or mild objective symptoms without any of the aforementioned symptoms.

In cases, in which the allergist deemed an allergic cause of the reaction possible, skin test were performed with the Covid-19 vaccine and the excipients PEG and Polysorbate 80.

The study was approved by the Medical Ethical Committee of the UMCG and the participating centers (METC number COVID19 vaccine hypersensitivity: 202100445) and written informed consent was waived. Statistical analyses were performed using SPSS, version 27.

RESULTS

In total, 390 persons (89% females, mean age of 49±16 years) were vaccinated in the hospital. 303 (78%) persons were referred because they had reacted adversely within four hours after a previous COVID-19 vaccination, of which 67 (22%) were treated with epinephrine. Fourteen patients were referred because of an allergy to one the excipients of the COVID-19 vaccine. Of the 390 persons, 154 (39.5%) had comorbidity of allergic rhinitis and/or asthma, 24 (6.2%) had chronic urticaria, and 5 (1.3%) had an underlying mast cell disorder.

Of the 303 persons that reacted to a Covid-19 vaccine, 112 (28.7%)had a moderate to severe reaction. These moderate to severe reactions presented with the following symptoms: generalized urticaria/erythema (n=51; 13.1%), angioedema (n= 56; 14.4%), hypotension (n=17; 4.4%), or stridor/decrease of oxygen saturation (n=15; 3.8%). 166 persons (42.5%) reacted mildly experiencing: a tight throat, shortness of breath, localized skin rash, itch, tingling sensation or numbness of skin, abdominal pain, vomiting and/or diarrhea, rhinorrhea/conjunctivitis, malaise, decreased alertness, headache, dizziness or palpitations.

Of the 390 persons that were vaccinated, 387 received a full dose of the vaccination. Most persons received a Comirnaty vaccination (358/387=93%), 29 persons received different vaccines because of various reasons.

Of the 387 persons fully vaccinated in hospital, 77 persons reacted adversely. Six of the 387 persons (1.6%) that received a full dose in the hospital had a moderate to severe immediate reaction that were treated with epinephrine, and two of them were observed for an extended amount of time (table). Notably 4 of these 6 persons had severe reactions in the past to a previous administration of a Comirnaty vaccine, 1 had anaphylaxis to several drugs and a different (unknown) vaccine and 1 person had anaphylaxis to food. In 5/6 patient's tryptase was assessed during the reaction but in none it was elevated. In none of the 6 patients an allergic reaction was diagnosed. In retrospection, the two patients responding to food and drugs/ vaccines respectively epinephrine was given out of precaution.

71 persons had a 'mild' reaction that was less severe, or as severe as the previous reaction. 67 persons were treated with epinephrine out of the hospital due to an adverse reaction following a previous COVID-19 vaccination All of them were revaccinated: 44 (64.7%) with the same vaccine, 6 (9.0 %) with another vaccine,

the remaining with another vaccine because of other/logistic reasons. In 25/67 (37.3%) persons, symptoms were reported for which 11/25(28%) persons received treatment. None of these 67 persons had a moderate – to severe immediate reaction.

The value of skin tests was limited, as neither a positive nor a negative the skin test result could predict whether a patient would respond to the vaccine with an adverse reaction, also shown in other studies (Wolfson et al, Greenhawt et al).

DISCUSSION

Only 6 of 387 (1.6%), reacted moderately to severely to a COVID-19 vaccine after a previous reaction. 4 of these 6 persons have reacted severely on the previous dose. A severe immediate reaction, consisting of anaphylaxis or objectived angioedema on a Covid-19 vaccine therefore seems the only risk factor for a moderate to severe reaction on a following dose. All other patients reacted mildly or not at all and never needed epinephrine.

Most persons that had a reaction on a Covid-19 vaccine, treated with epinephrine, did not need treatment on a second dose. Some of these non-life threatening symptoms may be perceived as severe and treated by health care workers with epinephrine. As long as the person is not wheezing, you can converse normally with a person pulse and blood pressure are within normal limits it is often better to reassure the patient and do not give any treatment. Therefore we advise only referring persons to an allergist in case of objectived angioedema or anaphylaxis after a previous Covid-19 vaccine. Although In daily practice, it will be hard to implement this advice because most healthcare workers that administer the vaccines, have no experience in distinguishing between reactions that are truly life-threatening and those that appear life-threatening.

Reference list

Alhumaid S, Al Mutair A, Al Alawi Z, Rabaan AA, Tirupathi R, Alomari MA, Alshakhes AS, Alshawi AM, Ahmed GY, Almusabeh HM, Alghareeb TT, Alghuwainem AA, Alsulaiman ZA, Alabdulmuhsin MA, AlBuwaidi EA, Dukhi AKB, Mufti HN, Al-Qahtani M, Dhama K, Al-Tawfiq JA, Al-Omari A. Anaphylactic and nonanaphylactic reactions to SARS-CoV-2 vaccines: a systematic review and meta-analysis. Allergy Asthma Clin Immunol. 2021 Oct 16;17(1):109. doi: 10.1186/s13223-021-00613-7.

Jaggers J, Samarakoon U, Fu X, Gonzalez-Estrada A, Anvari S, Chong HJ, Van Meerbeke SW, Petrov AA, Chow TG, Banerji A, Judd A, Blumenthal KG.J Allergy Clin Immunol Pract. 2022 Nov;10(11):3020-3023. doi: 10.1016/j.jaip.2022.08.008. Epub 2022 Aug 12.PMID: 35964925

Abbaspour S, Robbins GK, Blumenthal KG, Hashimoto D, Hopcia K, Mukerji SS, Shenoy ES, Wang W, Klerman EB.Vaccines (Basel). 2022 Oct 19;10(10):1747. Identifying Modifiable Predictors of COVID-19 Vaccine Side Effects: A Machine Learning Approach doi: 10.3390/vaccines10101747.PMID: 36298612

Chu DK, Abrams EM, Golden DBK, Blumenthal KG, Wolfson AR, Stone CA Jr, Krantz MS, Shaker M, Greenhawt M.JAMA Intern Med. 2022 Apr 1;182(4):376-385. Risk of Second Allergic Reaction to SARS-CoV-2 Vaccines A Systematic Review and Meta-analysis doi:10.1001/jamainternmed.2021.8515.PMID: 35188528

Krantz MS, Kwah JH, Stone CA Jr, Phillips EJ, Ortega G, Banerji A, Blumenthal KG. Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose. JAMA Intern Med. 2021 Nov 1;181(11):1530-1533. doi: 10.1001/jamainternmed.2021.3779.PMID: 34309623

Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X, Wickner P, Samarakoon U, Saff RR, Blumenthal KG, Banerji A.J Allergy Clin Immunol Pract. 2021 Sep;9(9):3308-3320.e3. doi: 10.1016/j.jaip.2021.06.010. Epub 2021 Jun 22.PMID: 34166844

Greenhawt M, Shaker M, Golden DBK, Abrams EM, Blumenthal KG, Wolfson AR, Stone CA Jr, Krantz MS, Chu DK, Dwamena BA. Allergy. 2023 Jan;78(1):71-83. doi: 10.1111/all.15571. Epub 2022 Nov 23.PMID: 36321821

Table. Results for persons whom received epinephrine at the hospital site (n=6)

Study number	18 (UMCG)	67 (UMCU)	155 (EMC)	168 (UMCG)	193 (UMCG)	194 (UMCG)
Gender	Female	Female	Female	Female	Female	Female
Age	24	29	28	52	43	43
Reason of vaccination in a hospital setting	Anaphylaxis to previous COVID-19 (Comirnaty) vaccine	Anaphylaxis to several food products	first COVID-19 (Comirnaty) vaccine	Reaction to previous COVID-19 (Comirnaty) vaccine in person with severe poorly controlled asthma and drug-related anaphylaxis in medical history	Reaction to previous COVID-19 (Comirnaty) vaccine	Anaphylaxis to several drugs (including vaccines)
Reaction after vaccination dose (no.)	1	first Covid vaccine ever	1	1	1	First Covid vaccine ever
Symptoms (objective)before referral	Conjunctivitis; hypotension (systolic BP 80mmHg while normally around 120mmHg)	N/A	Itchy red skin rash, shortness of breath, nausea and diarrhea	Generalized urticaria Stridor/ decreased O2	Objective facial angioedema	N/A
Symptoms (subjective) before referral	Globus pharyngeus/sense of swollen throat; hoarseness; dyspnea; nausea; dizziness	N/A	Globus pharyngeus/sense of swollen throat Locoregional skin rash	Globus pharyngeus/sense swollen throat	Globus pharyngeus/ sense of swollen throat-dyspnea/ dizziness	N/A
Medication for reaction, before referral	Antihistamines iv Corticosteroid iv Epinephrine im	N/A	Antihistamines iv epinephrine im	Antihistamines iv Epinephrine im	Antihistamines iv Epinephrine im	N/A

Study number	18 (UMCG)	67 (UMCU)	155 (EMC)	168 (UMCG)	193 (UMCG)	194 (UMCG)
Skin test performed	COVID-19 polysorbaat 80 PEG3500 PEG6000	PEG3500 Polysorbaat 80: Trometamol	Covid 19 Trometamol Polysorbaat 80 PEG3500 PEG4000	Not performed because of daily use of prednisone, clemastine, montelukast, imatinib and mepolizumab	None	None
Skin test result positive	COVID-19 Pfizer SPT undiluted positive	PEG(SPT) and PEG (ICT)	COVID-19 1:100 and1:10 PEG (ICT0	N/A	N/A	N/A
Name vaccine in the hospital	Moderna	Comirnaty	Comirnaty	Comirnaty	Comirnaty	Comirnaty

Study number	18 (UMCG)	67 (UMCU)	155 (EMC)	168 (UMCG)	193 (UMCG)	194 (UMCG)
Symptoms after in hospital vaccination	Conjunctivitis, rhinitis, hoarseness and (subjective) globus pharyngeus	Local erythema, itch, tingling tongue, nausea malaise, sputum, vomiting, inspiratory stridor (preexistent) dyspnoe, wheezing, globus feeling	Shortness of breath Itch Local urticaria	(additional premedication with clemastine 2mg iv, salbutamol inh) Local erythema, dizziness, novel wheezing for which salbutamol was readministered. After 3rd and last incremental step direct and quickly progressing erythema chest, arms, face, sense of doom with tachycardia for which 1st epinephrine was administered. 2nd dose was administered when symptoms returned after 20 minutes AND BP to 110/65, previously 140/70	(sense of) swollen throat, facial erythema, chest pain, dyspnea, tachycardia	(sense of) swollen throat, dyspnea, headache, nausea
Reason for epinephrine	Insufficient response to clemastine i.v. and wish to complete vaccination (was incrementally administered)	Increase of nausea and vomiting, despite levocetirizine, salbutamol, + metoclopramide+ prednisolone	Urticaria	direct and quickly progressing erythema chest, arms, face, sense of doom with tachycardia, later also decrease of BP	combination of the above	Combination of the above, quickly progressing despite clemastine

Study number	18 (UMCG)	67 (UMCU)	155 (EMC)	168 (UMCG)	193 (UMCG)	194 (UMCG)
Response to epinephrine	Relief of symptoms	yes	No response	Relief of symptoms	Partial relief of symptoms	Relief of symptoms
Tryptase (reference <11.4 ug/L)	2.92 2.46 ug/L (after)	3.4 ug/L	6.2 ug/L	6.104.97 ug/L	2.84 ug/L	Not measured
Interpretation of symptoms (type 1 allergy/ adverse side effect/ other)	CARPA or CAS-related	No allergic reaction, respiratory complaints in a person known with asthma (bronchial hyperreactivity)	No allergic reaction, Urticaria in person with known urticaria	Suspicion of type 1 allergy to PEG (because of combination with other severe drug allergies) but this could not be tested; alternatively, IRSS in a person with severe uncontrolled asthma and also susceptible to contact urticaria	Most likely hyperventilation (arterial blood gas confirmed this) and stress, at the index reaction combined with facial angioedema in a person with known U/A	Other (stress-related)

BP: blood pressure, CARPA: complement activation-related pseudoallergy, CAS: contact activation system, ISRR: immunization stress-related response, N/A: not applicable, PEG: polyethylene glycol, U/A: urticaria and/or angioedema