bijwerkingen centrumlareb

Overview of anaphylaxis and allergic reactions following COVID-19 immunisation

1. Introduction

For the pandemic vaccination campaign in 2021, four COVID-19 vaccines have been authorised and used for immunisation against SARS-CoV-2 infection in the Netherlands: the mRNA vaccines of Pfizer/BioNTech (Comirnaty®) [1] and Moderna (SpikeVax®) [2] and the adenovirus vector vaccines of Oxford/AstraZeneca (Vaxzevria®) [3] and Janssen (Jcovden®) [4]. These vaccines have been used during the vaccination campaign in different populations and in different numbers. Until 15 May 2022, 36 million vaccines were administered (Pfizer 25 million, Moderna 8 million, AstraZeneca 2.8 million, Janssen 0.8 million), for immunisation of approximately 13 million people. About 9.2 million people received three or more doses, 3.8 million people received two doses and 0.4 million people only had one dose [5].

The platforms used in mRNA vaccines were new and the pegylated nanoparticles were suspect to elicit acute allergic reactions in susceptible people [6]. An early study mentioned 11.1 per million reported cases of anaphylaxis within 15-30 minutes following the first administration of Comirnaty® in USA healthcare professionals [7], which was more than the estimated rate of 1.3 per million cases of anaphylaxis following any immunisation in general [8]. The possibility for an increased rate of serious allergic reactions to vaccines based on new platforms led to the obliged 15 minute observation time following each COVID-19 vaccine immunisation [9].

Anaphylaxis is defined by the World Allergy Organisation as a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes [10]. The most common mechanism for anaphylaxis is IgE-mediated allergic reaction to a variety of allergens, such as medications, foods and insect venoms; also called type I allergic reaction according to Gell and Coombs [11]. After re-exposure to a specific antigen, IgE crosslinking with high affinity receptors on basophils and mast cells results in rapid release of mediators causing immediate symptoms of pruritus, urticaria, angioedema, bronchospasm, hypotension and/or collapse (shock). As a response, heart rate increases. To confirm an IgE-mediated allergic reaction, sensibilisation to an allergen can be tested with skin prick tests. If a skin prick test is negative, a positive provocation test can confirm the diagnosis of a hypersensitivity reaction. However, the pathophysiological mechanism remains unknown. Non-IgE mediated mechanisms may be immunologic (e.g. activation of the complement system) and non-immunologic (e.g. direct mast cell activation or physical factors). When no clear cause or trigger can be identified, anaphylaxis is considered idiopathic [10].

The Brighton Collaboration (BC) case definition of anaphylaxis is a generally accepted list of criteria used to identify and classify reports of anaphylaxis on immunological products such as vaccines in pharmacovigilance. To classify the diagnostic certainty of a potential anaphylactic reaction, detailed information is needed about the nature, intensity, onset and duration of symptoms in relation to administration of the vaccine. In addition to the standard reporting form for adverse drug reactions to complete the required information, additional questions based on the BC case definition criteria were asked in all reports of anaphylaxis and severe allergic symptoms, see appendix A [12].

In this overview, reports with reactions that are suspected to be type I allergic reactions are discussed in five main categories: 1) ***anaphylaxis (including anaphylactic shock)*** according to the Brighton Collaboration case definition, 2) ***allergic reactions*** with multiple symptoms but not meeting the BC anaphylaxis criteria, 3) ***aggravation*** of existing allergies and ***post-acute allergic reactions*** to other substances, 4) ***angioedema*** with typical swellings and not part of anaphylaxis or allergic reaction, 5) ***urticaria*** which are not part of anaphylaxis or allergic reaction. Not included in this overview are various skin rashes and other conditions with other allergic mechanisms.

2. Anaphylaxis

Until 23 May 2022, The Netherlands Pharmacovigilance Centre Lareb received 90 unique spontaneous reports of anaphylactic reaction (n=73) or anaphylactic shock (n=17) with COVID-19 vaccines, including two from marketing authorisation holders (MAH). Report and patient characteristics are summarized in table 1.

Table 2.1 Report and patient characteristics of reports of anaphylaxis and anaphylactic shock following COVID-19 vaccines.

	Total	Pfizer	Moderna	Astra-Zeneca	Janssen	Unspecified vaccine
Reports (n)	90	58	18	10	3	1
- dose 1	73 (81.1%)	44 (75.9%)	15 (83.3%)	10 (100%)	3 (100%)	1 (100%)
- dose 2	12 (13.3%)	11 (19.0%)	1 (5.6%)			
- dose 3	5 (5.6%)	3 (5.2%)	2 (11.1%)			
Serious (n,% of all)[1]	74 (82.2%)	50 (86.2%)	13 (72.2%)	10 (100%)	1 (33%)	0
- Fatal	0	0	0	0	0	0
- Life threatening	54 (60%)	34 (58.6%)	11 (61.1%)	8 (80%)	1 (33%)	0
- Hospitalisation	19 (21.1%)	16 (27.6%)	2 (11.1%)	1 (10%)	0	0
- Other	12 (13.3%)	9 (15.5%)	1 (5.6%)	2 (20%)	0	0
Reporter (n,%)						
- Healthcare prof.	46 (51.1%)	29 (50%)	10 (55.6%)	4 (40%)	2 (67%)	1 (100%)
- Consumer	44 (48.9%)	29 (50%)	8 (44.4%)	6 (60%)	1 (33%)	0
Sex and age						
- female (n,%)	79 (87.8%)	51 (87.9%)	15 (83.3%)	10 (100%)	2 (67%)	1 (100%)
- male (n,%)	11 (12.2%)	7 (12.1%)	3 (16.7%)	0	1 (33%)	0
- Age (mean, range)	43.1 (17-91)	43.4 (17-91)	41.9 (18-58)	46.4 (24-65)	40.3 (30-54)	26 (26)
Time to onset (n,%)						
- < 15 minutes	58 (64.4%)	39 (67.2%)	12 (66.7%)	4 (40%)	3 (100%)	0
- 15-30 minutes	9 (10%)	4 (6.9%)	1 (5.6%)	4 (40%)	0	0
- < 1 day (> 30 min.)[2]	16 (17.8%)	11 (19.0%)	3 (16.7%)	1 (10%)	0	1 (100%)
- > 1 day	6 (6.7%)	3 (5.2%)	2 (11.1%)	1 (10%)	0	0
- Not exactly known	1 (1.1%)	1 (1.7%)	0	0	0	0
Outcome						
- Recovered/ Recovering	76 (84.4%)	44 (75.9%)	18 (100%)	10 (100%)	3 (100%)	1 (100%)
- Not recovered/ unknown	14 (15.6%)	14 (24.1%)	0	0	0	0
Patient						
- Healthcare worker	16 (17.8%)	7 (12.1%)	2 (11.1%)	6 (60%)	1 (33%)	0
- past COVID-19	7 (7.8%)	6 (10.3%)	0	1 (10%)	0	0
- Allergy history	64 (71.1%)	43 (74.1%)	11 (61.1%)	7 (70%)	3 (100%)	0
- Injection site reaction	14 (15.6%)	10 (17.2%)	1 (5.6%)	3 (30%)	0	0
- Recurrence[3]						
- - dose 2	7 (58.3%)	6 (54.5%)	1 (100%)	0	0	0
- - dose 3	3 (60%)	2 (67%)	1 (50%)	0	0	0

[1]CIOMS criteria for seriousness: more than one criterium can be reported per report; hospitalisation includes > 24 hours admission. [2]Time to onset (TTO) '< 1 day but > 30 min' includes 'within 1 day'. [3]Recurrence includes reports in which allergic symptoms following a previous COVID-19 vaccine were reported, i.e. 7 out of 12 second dose reports mentioned to have had allergic symptoms with the first dose as well; the 3 reports of dose 3 experienced allergic symptoms with all three doses.

Reports

The majority of anaphylactic reactions occurred following a first dose of any vaccine. By the nature of the condition, almost all reports (82.2%) were considered as serious, according to one of the CIOMS criteria. One fifth was hospitalised for more than 24 hours, but in the reports short hospitals stays were mentioned as well. Half of the reports was reported by healthcare professionals. If cases were reported in duplicate or triplicate (by consumers and one or more physicians), additional information was added to the best documented case, which was considered master and this reporter is counted.

Brighton Collaboration case levels

Based on available information, in 35 (38.9%) reports criteria for level 1 of diagnostic certainty were met and in 29 (32.2%) reports level 2 was met. In 26 (28.9%) reports anaphylaxis was reported but additional information on symptoms, course and/or treatment was insufficient, indicated as level 4/5.

Sex and age

In 79 (87.8%) of the cases, the patient was female. The mean age for men and women was equal, about 43 years, with a range of 17-91 years. The majority of people experiencing anaphylaxis following COVID-19 immunisation were age between 20 and 60 years, as is shown in figure 2.1.

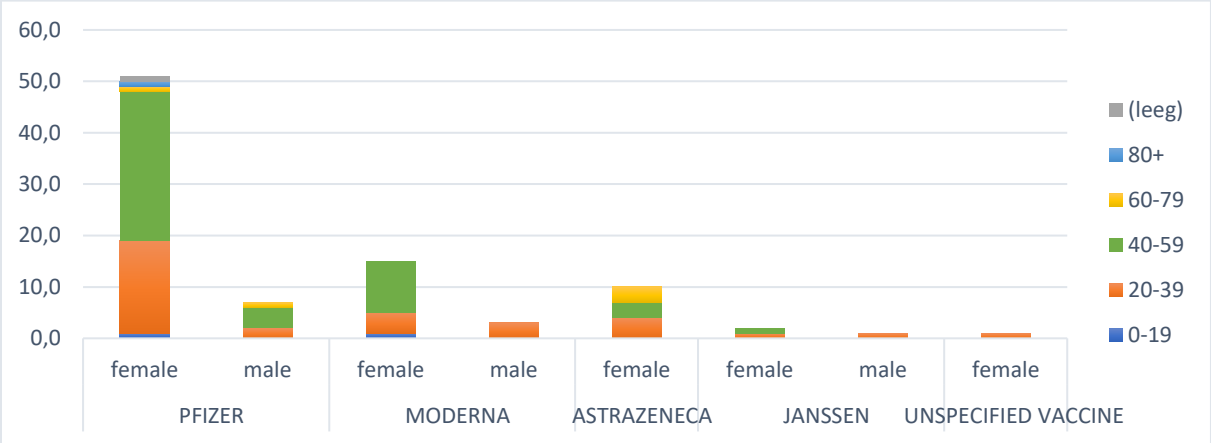

Figure 2.1: Distribution of the number of reports of anaphylaxis with COVID-19 vaccines stratified per vaccine, sex and age group.

Time to onset (TTO) and accompanying causes

In 58 (64.4%) of the reports anaphylaxis occurred within 15 minutes following vaccination and in another 10% the reaction started in 15-30 minutes. In 16 reports anaphylaxis occurred within one day but after 30 minutes: in 6 reports the exact TTO is unknown and in 10 reports TTO varied from 1.5 to 24 hours. In one of these late cases, consumption of shrimp may have caused food allergy.

Of the six reports with latencies longer dan 24 hours, in five another eliciting factor was involved. Four had a reaction to a drug for which they never had been allergic before; amoxicillin/clavulanic acid (2), ibuprofen (1), medroxyprogesterone (1). One had anaphylaxis following eating nuts, for which a mild allergy was known but was not associated with anaphylaxis before. One had new onset of recurrent anaphylaxis (17, 31 and 45 days following vaccination), without a clear eliciting factor.

Treatment and outcome

Reported treatments were adrenaline (as EpiPen® or other injection) in 73 (81.1%), antihistamines (mainly clemastine injections) in 70 (77.8%), corticosteroids in 39 (43.3%), inhalation medication such as salbutamol or ipratropium in 13 (14.4%), oxygen in 6 (6.7%) in 10 reports (11.1%) treatment was

not specified. At time of reporting, 76 (84.4%) had recovered or was recovering after adequate treatment. No cases with fatal outcome were reported. No specific information on ICU admission or 'near fatal' cases is available, apart from hospitalisation in 19 (21%) of the cases.

Recurrence

In 7 reports following a second and in 3 reports following a third dose, allergic symptoms had also occurred with a previous doses. It concerns nine women and one man, aged 17-53 years, with the Pfizer (8) and Moderna (2) vaccines with homologous vaccine sequences in all cases. None reported a confirmed anaphylaxis with a previous dose, but the following symptoms were mentioned: rash/erythema/pruritus in 6 reports, swellings/ angioedema/throat tightness in 5 reports, dyspnoea in 4 reports and urticaria in 2 reports. To note, the Dutch immunisation guidelines contraindicated a next dose if a severe or acute suspected allergic reaction occurred within 4 hours after vaccination [9].

Allergy history

In 64 reports (71.1%) one or more allergic conditions in the patient's medical history were reported. These include drug allergies (36), food allergies (23), insect sting allergies (8), asthma (12), hay fever (6), urticaria (3), allergy to animals (4), histamine intolerance (3), latex allergy and multiple not specified allergies (6). Of those with drug allergies, 3 patients had had a previous anaphylactic reaction to another vaccine (not COVID) in the past.

Other patient characteristics

A previous SARS-CoV-2 infection was reported in 7 (7.8%) of all cases. Sixteen (17.8%) patients were healthcare workers. Injections site reactions (inflammation, erythema, swelling, pruritus, pain) were reported in 14 (15.6%) cases .

Reporting rates

The *first dose* reporting rates for anaphylaxis, of which diagnostic certainty is based on the Brighton Collaboration case definition criteria, varies from 1.3 per million administered doses for Janssen, 5.0 per million for AstraZeneca, 7.6 per million for Moderna to 4.5 per million for Pfizer. See figure 2.2.

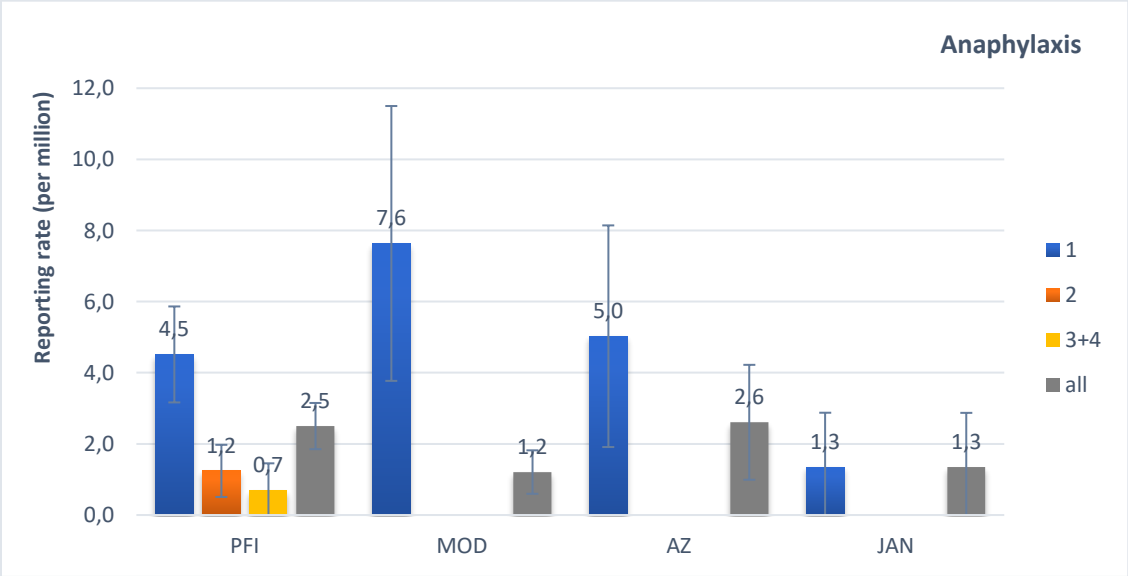

Figure 2.2: Reporting rates in number per million administered doses (95% CI) of anaphylaxis with COVID-19 vaccines, per dose and as total.

Discussion anaphylaxis

In this section, only reports that met the Brighton Collaboration case definition criteria for anaphylaxis (including anaphylactic shock) were included. The BC criteria indicate the level of diagnostic certainty of anaphylaxis. However, there are three important limitations of the BC case definition for anaphylaxis, that may lead to misclassification of cases and an underestimation of true anaphylaxis cases.

- The first limitation is use of the impractical criteria such as 'delayed capillary refill time' as a minor cardiovascular criterium, which is not a routine diagnostic action.
- The second limitation concerns misclassification of 'non serious and localised angioedema of respiratory mucosal tissues' as level 1 anaphylaxis, since it applies to both skin and cardiovascular criteria. To note, we only included reports with *more than one* symptom to evaluate the diagnostic certainty of anaphylaxis.
- The third limitation concerns misclassification of cases with limited documentation as 'no anaphylaxis' due to lack of information on blood pressure and heart rate in patients with 'urticarial rash and collapse'.

Another difficulty in assessing cases of anaphylaxis is to distinguish the event from differential diagnostic conditions, such as syncope, anxiety and panic attack, hyperventilation or vasovagal reactions related to vaccination procedure rather than the vaccine.

3. Allergic reactions following vaccination

Until 23 May 2022, The Netherlands Pharmacovigilance Centre Lareb received 298 unique spontaneous reports of combination of symptoms that are suspected of type I (IgE mediated) considered allergic reactions (but are *not* meeting criteria for anaphylaxis) following administration of COVID-19 vaccines, including 20 from marketing authorisation holders (MAH). For these reactions the MedDRA preferred term (PT) Hypersensitivity with lower level term (LLT) Allergic reaction was used exclusively in the assessment of the report. It includes reactions which were reported as anaphylaxis *or* severe allergic reaction *or* as a combination of typically allergic symptoms, but are not meeting de Brighton Collaboration case definition criteria for anaphylaxis. Single symptom reactions such as angioedema or urticaria are described separately below (paragraphs 5 and 6).

In the current set, allergic reactions after vaccination but likely triggered by other substances or as aggravation of existing allergic disease are excluded and discussed separately (see paragraph 4). Report and patient characteristics of allergic reactions to COVID vaccines are summarized in table 3.1.

Table 3.1 Report and patient characteristics of reports of allergic reactions, not meeting criteria for anaphylaxis, (coded as Meddra PT Hypersensitivity) following COVID-19 vaccines. Allergic reactions after vaccination but likely triggered by other substances or as aggravation of existing allergic diseases are excluded.

	Total	Pfizer	Moderna	Astra-Zeneca	Janssen	Unspecified vaccine
Reports (n)	298	196	49	41	10	2
- dose 1	198 (66.4%)	135 (68.9%)	16 (32.7%)	36 (87.8%)	10 (100%)	1 (50%)
- dose 2	58 (19.5%)	40 (20.4%)	13 (26.5%)	5 (12.2%)	0	0
- dose 3	41 (13.8%)	21 (10.7%)	19 (38.8%)	0	0	1 (50%)
- dose 4	1 (0.3%)	0	1 (2.0%)	0	0	0
Serious (n,% of all)[1]	94 (31.5%)	69 (35.2%)	9 (18.4%)	13 (31.7%)	2 (20%)	1 (50%)
- Fatal	0	0	0	0	0	0
- Life threatening	57 (19.1%)	46 (23.5%)	4 (8.2%)	6 (14.6%)	1 (10%)	0
- Hospitalisation	11 (3.7%)	9 (4.6%)	1 (2.0%)	1 (2.4%)	0	0
- Other	31 (10.4%)	17 (8.7%)	6 (12.2%)	6 (14.6%)	1 (10%)	1 (50%)

Reporter (n,%)						
- Healthcare prof.	84 (28.2%)	62 (31.6%)	11 (22.4%)	10 (24.4%)	10 (100%)	2 (100%)
- Consumer	214 (71.8%)	134 (68.4%)	38 (77.6%)	31 (75.6%)	0	0
Sex and age						
- female (n,%)	254 (85.2%)	169 (86.2%)	40 (81.6%)	35 (85.4%)	8 (80%)	2 (100%)
- male (n,%)	43 (14.4%)	27 (13.8%)	9 (18.4%)	6 (14.6%)	1 (10%)	0
- unknown (n,%)	1 (0.3%)	0	0	0	1 (10%)	0
- Age (mean, range)	45.8 (13-91)	44.0 (13-91)	50.2 (19-82)	48.1 (19-64)	43.0 (18-54)	34.0 (33-35)
Time to onset (n,%)						
- < 15 minutes	111 (37.2%)	73 (37.2%)	19 (38.8%)	18 (43.9%)	1 (10%)	0
- 15-30 minutes	27 (9.1%)	18 (9.2%)	7 (14.3%)	1 (2.4%)	1 (10%)	0
- < 1 day (> 30 min.)	104 (34.9%)	72 (36.7%)	17 (34.7%)	12 (29.3%)	2 (20%)	1 (50%)
- > 1 day	48 (16.1%)	29 (14.8%)	6 (12.2%)	8 (19.5%)	5 (50%)	0
- Not exactly known	8 (2.7%)	4 (2.0%)	0	2 (4.9%)	1 (10%)	1 (50%)
Outcome						
- Recovered/ Recovering	226 (75.8%)	155 (79.1%)	35 (71.4%)	30 (73.2%)	5 (50%)	1 (50%)
- Not recovered/ unknown	72 (24.2%)	41 (20.9%)	14 (28.6%)	11 (26.8%)	5 (50%)	1 (50%)
Patient						
- Healthcare worker	44 (14.8%)	25 (12.8%)	5 (10.2%)	13 (31.7%)	1 (10%)	0
- past COVID-19	36 (12.1%)	28 (14.3%)	4 (8.2%)	2 (4.9%)	2 (20%)	0
- Allergy history	171 (57.3%)	117 (59.7%)	31 (63.3%)	19 (46.3%)	3 (30%)	1 (50%)
- Injection site reaction	69 (23.1%)	37 (18.9%)	18 (36.7%)	12 (29.3%)	2 (20%)	0
- Recurrence (n,% dose)[2]						
- - dose 2	23 (39.7%)	14 (35.0%)	6 (46.2%)	3 (60%)	0	0
- - dose 3	9 (22.0%)	5 (23.8%)	3 (15.8%)	0	0	1 (100%)
- - dose 4	0	0	0	0	0	0

[1]CIOMS criteria for seriousness: for each case more than one criterium can be reported; hospitalisation includes > 24 hours admission. TTO '< 1 day but > 30 min' includes 'within 1 day'. [2]Recurrence includes reports in which allergic symptoms following a previous COVID-19 vaccine also were reported, i.e. with a second dose 23 out of 58 reported any allergic symptom with the first dose as well.

Reports

The majority allergic reactions (combination of symptoms *not* meeting anaphylaxis criteria) occurred following a first dose of any vaccine. One-third of these reports (82.2%) were considered serious, according to one of the CIOMS criteria: 19% was considered life threatening, 3.7% was hospitalised for more than 24 hours and 10% was considered for other reasons. Twenty-eight percent of the reports was reported by healthcare professionals. If cases were reported in duplicate or triplicate (by consumers and one or more physicians), all the information was added to the best documented case, which was considered master and this reporter is counted.

Brighton Collaboration case levels

In 32 (10.7%) reports, the reaction or symptoms were reported as anaphylaxis by the reporter. However, the available information in the report was insufficient or indicated that the BC case definition criteria for anaphylaxis were not met. Therefore, these cases were coded as 'allergic reaction' instead of 'anaphylaxis'.

Sex and age

In 254 (85.2%) of the cases, the patient was female. The mean age for men and women was equal, about 45 years, with a range of 13-91 years. The majority of people experiencing allergic reactions following COVID-19 immunisation were aged between 20 and 60 years, as is shown in figure 3.1.

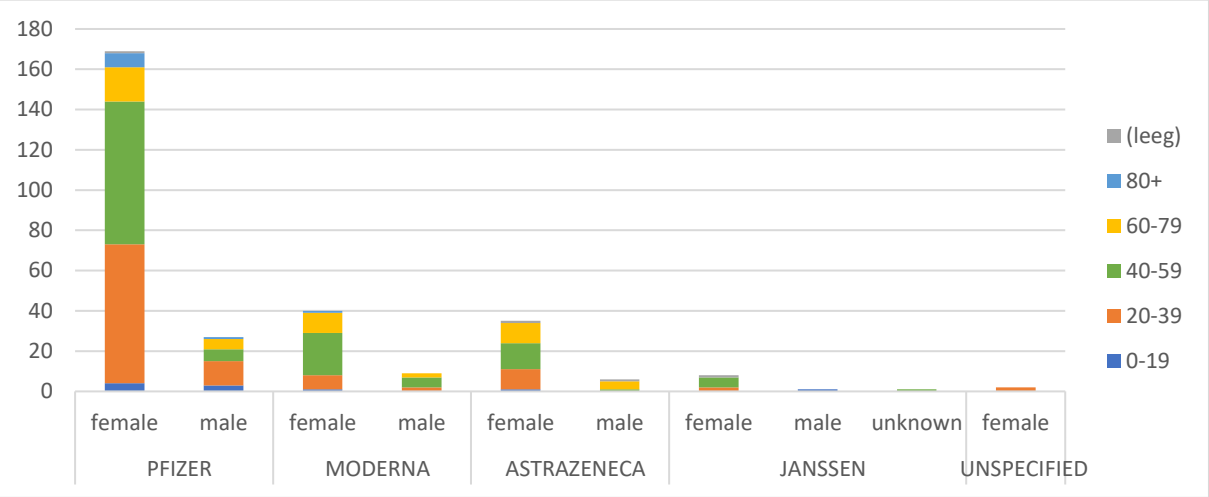

Figure 3.1: Distribution of the number of reports of allergic reactions (not anaphylaxis) with COVID-19 vaccines stratified per vaccine, sex and age group.

Time to onset (TTO)

In 111 (37.7%) of the reports the allergic reaction occurred within 15 minutes following vaccination and in another 27 (9.1%) the reaction started in 15-30 minutes. In 104 (34.9%) reports the allergic occurred within one day but after 30 minutes. In 48 reports (16.1%) the allergic reaction after 1 day and 8 reports (2.7%) the time to onset is not known.

Of the reports with long latencies (> 1 day), the time to onset varied from 28 hours to 5 months, with a median of 6 days (IQR 3-8 days). In these reports no specific eliciting factor or additional cause was mentioned.

Treatment and outcome

Reported treatments were adrenalin (as EpiPen® or other injection) in 71 (23.8%), antihistamines (clemastine injections and oral antihistamines) in 191 (64.1%), corticosteroids in 48 (16.1%), inhalation medication such as salbutamol or ipratropium in 11 (3.7%), oxygen in 1 (0.3%) in 28 reports (9.4%) treatment was not specified. At time of reporting, 226 (75.8%) had recovered or was recovering after adequate treatment. No cases with fatal outcome were reported.

Recurrence

In 23 reports following a second dose and in 9 reports following a third dose, allergic symptoms had also occurred with a previous doses. Of the nine persons with an allergic reaction following the 3rd dose, two had allergic symptoms with the 1st and 2nd dose, four had allergic symptoms with the 1st dose only and three had allergic symptoms with the 2nd dose only. It concerns 28 women and four men, aged 21-76 years, with Pfizer (19), Moderna (9), AstraZeneca (3) and an unspecified vaccine (1) with homologous vaccine sequences in all cases.

Allergy history

In 171 reports (57.4%) one or more allergic conditions in the patient's medical history were reported. These include drug allergies (87; 29.2%), food allergies (44; 14.8%), hay fever/pollen (28; 9.4%), allergy to animals/house dust (19; 6.4%), insect sting allergies (19; 6.4%), asthma (11; 3.7%), urticaria (5; 1.7%), multiple allergies (9; 3.0%) and other/not specified allergies (26; 8.7%). Of those with drug

allergies, 4 patients had had a previous allergic reaction to another vaccine (influenza (3) or MMR (1)) in the past.

Other patient characteristics

A previous SARS-CoV-2 infection was reported in 36 (12.1%) of all cases. Forty-four (14.8%) patients were healthcare workers; 31.7% with AstraZeneca, which was initially administered to a healthcare workers during the vaccination campaign. Injections site reactions (inflammation, erythema, swelling, pruritus, pain) were reported in 69 (23.1%) cases .

Reporting rates

The *first dose* reporting rates for potential type 1 allergic reactions (not meeting criteria for anaphylaxis) vary between 3.6 per million administered doses for Janssen up to 17.1 per million administered doses for AstraZeneca. See figure 3.2.

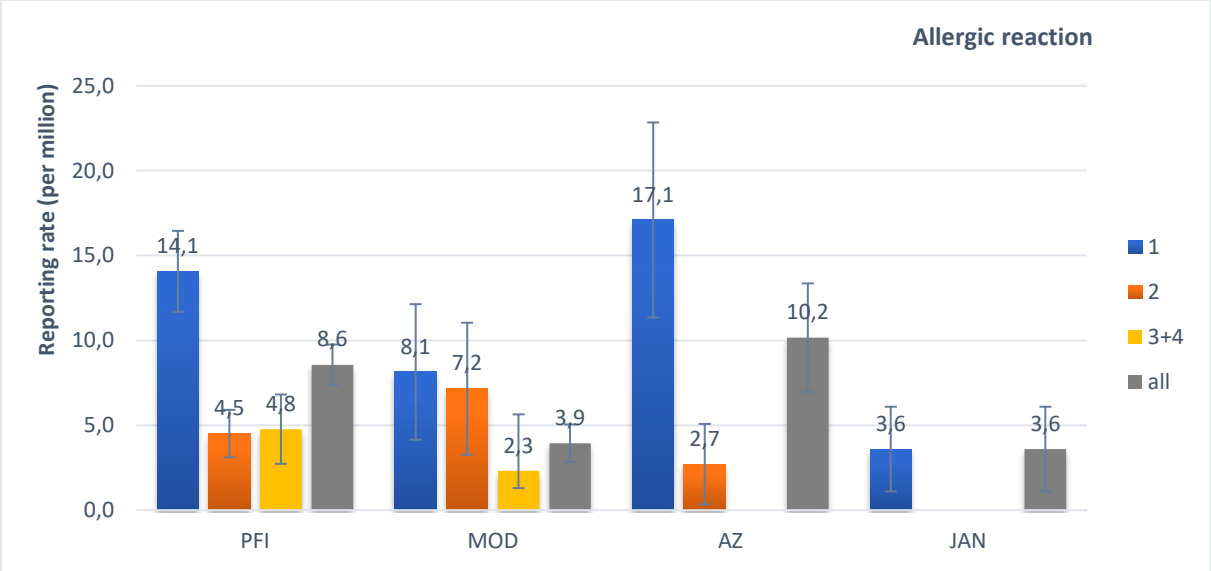

Figure 3.2: Reporting rates in number per million administered doses (95% CI) of allergic reaction (not meeting anaphylaxis criteria) with COVID-19 vaccines, per dose and as total.

4. Allergy aggravated and post-acute allergic reactions to other substances, *after* vaccination

A separate set of reports of hypersensitivity and allergic reactions, are patients who mentioned aggravation of already existing allergic conditions such as asthma or hay fever, chronic urticaria or certain allergies and patients who mention an allergic reaction to another substance, for which they were not allergic before.

Asthma

A total of 202 people reported ‘asthma’ following COVID-19 immunisation. This concerns 152 reports of aggravation of existing asthma, 17 of newly diagnosed asthma, 13 of return of asthma in patients who had no symptoms for years, 2 who had similar complaints with COVID-19 and 18 unspecified reports of asthma which were not further specified.

Table 4.1 Report and patient characteristics of asthma following COVID-19 vaccination

	Total	Pfizer	Moderna	Astra-Zeneca	Janssen	Unspecified vaccine
Reports (n)	202	116	42	35	8	1

- dose 1	111 (55.5%)	60 (51.7%)	14 (33.3%)	28 (80%)	8 (100%)	1 (100%)
- dose 2	65 (32.2%)	45 (38.8%)	13 (31.0%)	7 (20%)	0	0
- dose 3	26 (12.9%)	11 (9.5%)	15 (35.7%)	0	0	0
Serious (n,% of all)	19 (9.4%)	11 (9.5%)	5 (11.9%)	3 (8.6%)	0	0
Sex and age						
- female (n,%)	159 (78.7%)	93 (80.2%)	36 (85.7%)	25 (71.4%)	4 (50%)	1 (100%)
- male (n,%)	43 (21.3%)	23 (19.8%)	6 (14.3%)	10 (28.6%)	4 (50%)	0
- Age (mean, range)	48.1 (12-80)	45.6 (12-80)	50.2 (23-74)	54.9 (21-68)	45 (30-63)	39
Time to onset (n,%)						
- < 15 minutes	7 (3.5%)	4 (3.4%)	3 (7.1%)	0	0	0
- < 1 day (> 15 min.)	95 (47.0%)	52 (44.8%)	24 (57.1%)	18 (51.4%)	1 (12.5%)	0
- > 1 day	88 (43.6%)	55 (47.4%)	15 (35.7%)	13 (37.1%)	5 (41.7%)	0
- Not exactly known	11 (5.4%)	4 (3.4%)	0	4 (11.4%)	2 (25.0%)	1 (100%)
Outcome						
- Recovered/ Recovering	112 (55.4%)	61 (52.6%)	29 (69.0%)	17 (48.6%)	5 (62.5%)	0
- Not recovered/ unknown	89 (44.1%)	54 (46.6%)	13 (31.0%)	18 (51.4%)	3 (37.5%)	1 (100%)
- Fatal	1 (0.5%)	1 (0.9%)	0	0	0	0
Patient						
- Healthcare worker	34 (16.8%)	13 (11.2%)	8 (19.0%)	11 (31.4)	2 (25%)	1 (100%)
- past COVID-19	32 (15.8%)	20 (17.2%)	8 (19.0%)	1 (2.9%)	3 (37.5%)	1 (100%)
- Injection site reaction	73 (36.1%)	32 (27.6%)	27 (64.3%)	12 (34.3%)	2 (25%)	0
- Recurrence (n,% of 2nd /3rd dose)	22 (24.2%)	14 (25.0%)	6 (21.4%)	2 (28.6%)	0	0

The majority of the reports of asthma, consider the first dose and started within 1 day following the vaccination, however almost half the reports (44%) mention a longer time to onset (TTO). The mean TTO was 6.1 days (for all vaccines), with a range of 0-183 days. Of those reports with the second or third dose, 24% mentioned recurrence of the symptoms following two or more vaccinations.

Half of the patients recovered from asthma at time of reporting. There are few reports (n=15) that mention the duration of the reaction, varying from 1 hour to 6 weeks. In the majority of the reports, the duration is unknown. One patient died of asthmatic attack, four days after vaccination. According to the reporting physician, other causes, such as COVID-19 infection, asthma/COPD exacerbation or a cardiac event, could not be excluded.

Hay fever

A total of 60 people reported 'hay fever' following COVID-19 immunisation. This concerns 36 (60%) reports of aggravation or worse symptoms of already existing hay fever, 13 (21.7%) reports of new onset of hay fever, 5 (8.3%) reports of return of hay fever in patients who had no symptoms for years and 6 (10%) reports with an unspecified pattern of hay fever.

Table 4.2 Report and patient characteristics of hay fever following COVID-19 vaccination

	Total	**Pfizer**	**Moderna**	**Astra-Zeneca**	**Janssen**	**Unspecified vaccine**
Reports (n)	60	39	10	8	3	0
- dose 1	38 (63.3%)	25 (64.1%)	5 (50%)	5 (62.5%)	3 (100%)	0
- dose 2	18 (30%)	13 (33.3%)	2 (20%)	3 (37.5%)	0	0
- dose 3	4 (6.7%)	1 (2.6%)	3 (30%)	0	0	0

Serious (n,% of all)	0	0	0	0	0	0
Sex and age						
- female (n,%)	35 (58.3%)	23 (59.0%)	5 (50%)	4 (50%)	3	0
- male (n,%)	25 (41.7%)	16 (41.0%)	5 (50%)	4 (50%)	0	0
- Age (mean, range)	50.2 (21-80)	49.8 (23-80)	49.5 (38-68)	58 (36-65)	37.7 (21-55)	0
Time to onset (n,%)						
- < 15 minutes	2 (3.3%)	1 (2.6%)	0	1 (12.5%)	0	
- < 1 day (> 15 min.)	23 (38.3%)	17 (43.6%)	3 (30%)	3 (37.5%)	0	
- > 1 day	34 (56.7%)	20 (51.3%)	7 (70%)	4 (50%)	3 (100%)	
- Not exactly known	1 (1.7%)	1 (2.6%)	0	0	0	
Outcome						
- Recovered/ Recovering	20 (33%)	11 (28.2%)	4 (40%)	5 (62.5%)	2 (67%)	
- Not recovered/ unknown	40 (67%)	28 (71.8%)	6 (60%)	3 (37.5%)	1 (33%)	
Patient						
- Healthcare worker	6 (10%)	4 (10.3%)	0	1	1	
- past COVID-19	6 (10%)	5 (12.8%)	0	0	1	
- Injection site reaction	13 (21.7%)	6 (15.4%)	4 (40%)	3	0	
- Recurrence (n,% of 2nd /3rd dose)	4 (18.2%)	2 (14.3%)	2 (40%)	0	0	

The majority of reports of hay fever was reported following the first dose. About half of the reports of hay fever started within one day after vaccination. The mean time to onset (TTO) was 8.0 days, with a range of minutes after start to 117 days. Duration was mentioned in 4 reports, varying form 2 days to 1 month, although in the majority of the reports the duration was unknown at time of reporting. In four reports a recurrence of the hay fever symptoms occurred following two or three doses.

The main months of onset of hay fever symptoms following COVID-19 vaccination were June and July, corresponding with a high vaccination rate during the campaign [5]. Typical hay fever related allergens in these months are grasses [13]; in three reports specific grass pollen allergy was described, the others mentioned nonspecific ‘pollen allergy’ or ‘hay fever’.

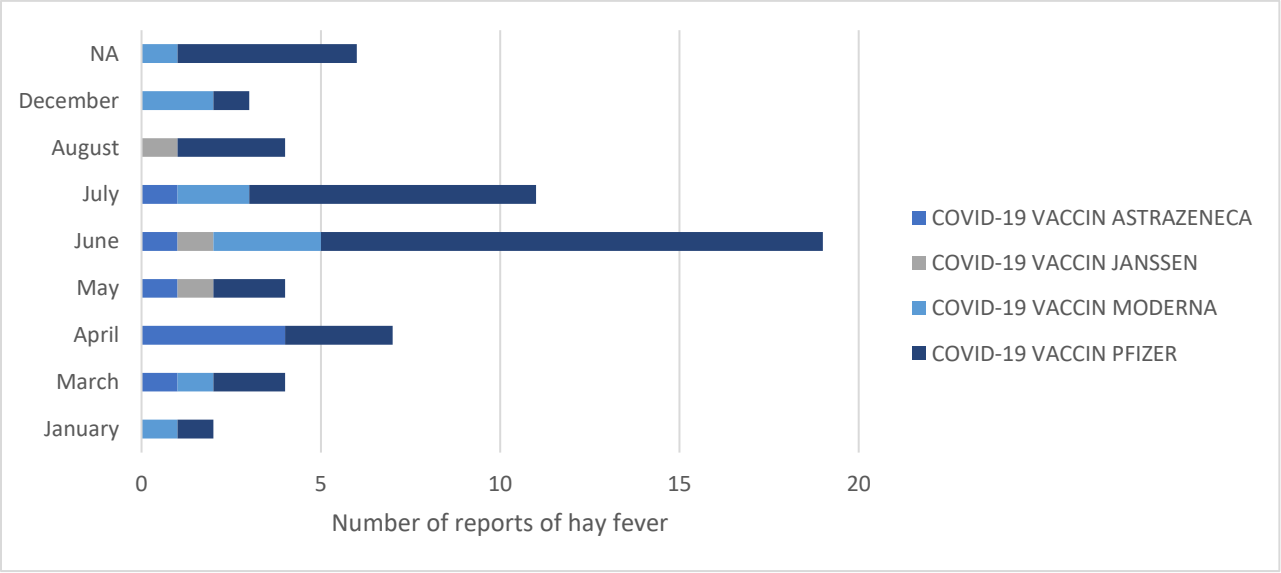

Figure 4.1 Distribution reports to start date (month) of hay fever following COVID-19 vaccination.

Other allergies: new onset or allergy aggravated

A total of 104 people reported to have had an allergic reaction, triggered by another substance, after the vaccination. This concerns:

- 83 reports of *new onset* of allergies: arthropod sting/bite (n=42), food (n=24), drug (n=10), others (n=6)
- 16 reports of *aggravation* of existing allergies: food (n=7), house dust mite (n=4), arthropod sting(n=2) and others (n=3)
- 2 reports of *return* of previously resolved allergies: drug allergy, allergy to animals
- 3 reports of unknown course of allergic reaction: arthropod bite (n=2), gluten sensitivity (n=1)

Table 4.3 Report and patient characteristics of aggravation or new onset of other allergies following COVID-19 vaccination

	Total	Pfizer	Moderna	Astra-Zeneca	Janssen	Unspecified vaccine
Reports (n)	104	74 (71.2%)	16 (15.4%)	9 (8.7%)	5 (4.8%)	0
- dose 1	53 (51.0%)	35 (47.3%)	7 (43.8%)	6 (66.7%)	5 (100%)	
- dose 2	44 (42.3%)	34 (45.9%)	7 (43.8%)	3 (33.3%)	0	
- dose 3	7 (6.7%)	5 (6.8%)	2 (12.5%)	0	0	
Serious (n,% of all)	11 (10.6%)	7 (9.5%)	2 (12.5%)	2 (22.2%)	0	
Sex and age						
- female (n,%)	80 (76.9%)	55 (74.3%)	12 (75%)	9 (100%)	4 (80%)	
- male (n,%)	24 (23.1%)	19 (25.7%)	4 (25%)	0	1 (20%)	
- Age (mean, range)	47.4 (13-89)	46.0 (13-89)	49.6 (23-67)	57.1 (24-67)	42.4 (37-54)	
Time to onset (n,%)						
- < 15 minutes	2 (1.9%)	0	0	1 (11.1%)	1 (20%)	
- < 1 day (> 15 min.)	19 (18.3%)	13 (17.6%)	5 (31.3%)	1 (11.1%)	0	
- > 1 day	79 (76.0%)	59 (79.7%)	11 (68.8%)	6 (66.7%)	3 (60%)	
- Not exactly known	4 (3.8%)	2 (5.7%)	0	1 (11.1%)	1 (20%)	
Outcome						
- Recovered/ Recovering	42 (40.4%)	25 (33.8%)	10 (62.5%)	4 (44.4%)	3 (60%)	
- Not recovered/ unknown	62 (59.6%)	49 (66.2%)	6 (37.5%)	5 (55.6%)	2 (40%)	
Patient						
- Healthcare worker	12 (11.5%)	7 (9.5%)	2 (12.5%)	2 (22.2%)	1 (20%)	
- past COVID-19	12 (11.5%)	8 (10.8%)	2 (12.5%)	1 (11.1%)	1 (20%)	
- Injection site reaction	17 (16.3%)	13 (17.6%)	3 (18.8%)	1 (11.1%)	0	
- Allergy history	45 (43.3%)	35 (47.3%)	5 (31.3%)	1 (11.1%)	4 (80%)	
- Recurrence (n,% of 2nd /3rd dose)	4 (7.8%)	3 (7.7%)	1 (11.1%)	0	0	

In 11 reports, a new allergic reaction was serious according to CIOMS criteria (7 life threatening, 2 hospitalisation, 2 other medically important condition): 5 drug allergies (NSAID n=3, antibiotic n=1, medroxyprogesterone n=1), 5 food allergies (nuts n=2, unspecified n=3), 1 arthropod sting allergy.

The majority of the reactions had a time to onset (TTO) of more than 1 day, with a mean of 15.9 days (range 0-174 days). These long latencies since vaccination can be explained by exposure to another substance as the allergen, and not the vaccine itself. In twelve reports, the duration is known and varies between 1 hour and 2 weeks; however in the majority the outcome and duration are unknown.

A medical history of any kind of allergic condition was reported in 43% of the cases. Few (7.8%) mentioned a recurrence of symptoms with multiple vaccine doses.

To note, the relatively large amount of cases of arthropod sting/bite allergy could be a misinterpretation of the occurrence of urticaria without the involvement of an insect or bug. In the reports of urticaria, some people thought to have had a severe reaction to an arthropod or insect sting but were later diagnosed as urticaria.

Discussion 'asthma, hay fever and other allergies'

As far as known from literature, there is no evidence for aggravation of asthma, hay fever or other allergies following COVID-19 vaccination. The prevalence of asthma and hay fever in Dutch general practitioner's registries is 107 and 49 per 1000 patients respectively. Based on the relatively low numbers of the reports of asthma (n=202) and hay fever (n=60) and the mass vaccination during the pollen season, coincidence of aggravation or new onset of these conditions in the period following vaccination cannot be ruled out [14-15]. Based on allergologist and immunologist practices, there has been no increase of aggravation or new onset of allergies in COVID-19 vaccinated people compared to not-vaccinated people [M. van Maaren, personal communication, 24-8-2022].

5. Angioedema

Until 23 May 2022, The Netherlands Pharmacovigilance Centre Lareb received 1772 spontaneous reports of any kind of angioedema (or angioedema related typical swellings) as a single symptom that were *not part* of anaphylaxis or allergic reaction (combination of symptoms as described above) following administration of COVID-19 vaccines, including 16 from marketing authorisation holders (MAH). Report and patient characteristics are summarized in table 5.1.

Table 5.1 Report and patient characteristics of reports of angioedema (not part of anaphylaxis or allergic reaction) following COVID-19 vaccines.

	Total	Pfizer	Moderna	Astra-Zeneca	Janssen	Unspecified vaccine
Reports (n)	1772	1169	307	209	85	2
- dose 1	1120 (63.2%)	739 (63.2%)	116 (37.8%)	178 (85.2%)	85 (100%)	2 (100%)
- dose 2	401 (22.6%)	310 (26.5%)	60 (19.5%)	31 (14.8%)	0	0
- dose 3	241 (13.6%)	119 (10.2%)	122 (39.7%)	0	0	0
- dose 4	10 (0.6%)	1 (0.1%)	9 (2.9%)	0	0	0
Serious (n,% of all)	43 (2.4%)	31 (2.7%)	7 (2.3%)	4 (2.3%)	1 (1.2%)	0
- Fatal	3 (0.2%)	2 (0.2%)	0	1 (0.5%)	0	0
- Life threatening	17 (1.0%)	10 (0.9%)	4 (1.3%)	2 (1.0%)	1 (1.2%)	0
- Hospitalisation	13 (0.7%)	10 (0.9%)	2 (0.7%)	1 (0.5%)	0	0
- Other	11 (0.6%)	10 (0.9%)	1 (0.3%)	0	0	0
Reporter (n,%)						
- Healthcare prof.	196 (11.1%)	139 (11.9%)	25 (8.1%)	23 (11.0%)	8 (9.4%)	1 (50%)
- Consumer	1576 (88.9%)	1030 (88.1%)	282 (91.9%)	186 (89.0%)	77 (90.6%)	1 (50%)
Sex and age						
- female (n,%)	1449 (81.8%)	964 (82.5%)	248 (80.8%)	171 (81.8%)	64 (75.3%)	2 (100%)
- male (n,%)	322 (18.2%)	204 (17.5%)	59 (19.2%)	38 (18.2%)	21 (24.7%)	0
- unknown (n,%)	1 (0.1%)	1 (0.1%)	0	0	0	0
- Age (mean, range)	49.6 (6-94)	48.5 (6-94)	52.5 (18-82)	54.7 (19-84)	41.5 (18-59)	66.5 (54-79)
Time to onset (n,%)						

- < 15 minutes	176 (9.9%)	132 (11.3%)	23 (7.5%)	17 (8.1%)	4 (4.7%)	0
- 15-30 minutes	121 (6.8%)	96 (8.2%)	15 (4.9%)	8 (3.8%)	2 (2.4%)	0
- < 1 day (> 30 min.)	994 (56.1%)	641 (54.8%)	182 (59.3%)	115 (55.0%)	56 (65.9%)	0
- > 1 day	467 (26.4%)	293 (25.1%)	83 (27.0%)	68 (32.5%)	21 (24.7%)	2 (100%)
- Not exactly known	14 (0.8%)	7 (0.6%)	4 (1.3%)	1 (0.5%)	2 (2.4%)	0
Outcome						
- Recovered/ Recovering	1194 (67.4%)	788 (67.4%)	216 (70.4%)	142 (67.9%)	48 (56.5%)	0
- Not recovered/ unknown	575 (32.4%)	379 (32.4%)	91 (29.6%)	66 (31.6%)	37 (43.5%)	2 (100%)
Patient						
- Healthcare worker	226 (12.8%)	122 (10.4%)	37 (12.1%)	43 (20.6%)	24 (28.2%)	0
- Past COVID-19	265 (15.0%)	176 (15.1%)	46 (15.0%)	28 (13.4%)	15 (17.6%)	0
- Allergy history	565 (31.9%)	399 (34.1%)	99 (32.3%)	46 (22.0%)	21 (24.7%)	0
- Injection site reaction	469 (26.5%)	282 (24.1%)	117 (38.1%)	53 (25.4%)	17 (20.0%)	0
- Recurrence (n,% dose)						
- - dose 2	106 (26.4%)	87 (28.1%)	10 (16.7%)	9 (29.0%)	0	0
- - dose 3	30 (12.4%)	16 (13.4%)	14 (11.5%)	0	0	0

CIOMS criteria for seriousness: for each case more than one criterium can be reported; hospitalisation includes > 24 hours admission. TTO '< 1 day but > 30 min' includes 'within 1 day'. Recurrence includes reports in which allergic symptoms following a previous COVID-19 vaccine also were reported, i.e. …

Reports

The majority of reactions with any kind of angioedema was reported following a first dose of any vaccine. Ninety percent of the reports were reported by consumers. 2.4% of the angioedema reactions was considered serious, according to one of the CIOMS criteria: 17 were considered life threatening, in 13 the patient was hospitalised for more than 24 hours, in 11 seriousness was considered for other reasons and in three reports the patient died. In these three reports with fatal outcome, none reported an allergic explanation for the symptoms and other causes and patient circumstances were present, such as cardiac failure and infection.

Sex and age

In 1449 (81.8%) of the cases, the patient was female. The mean age for men and women was 51.9 years (range 6-88) and 47.8 years (range 8-94) respectively. The majority of women experiencing angioedema following COVID-19 immunisation were aged between 40 and 59 years and men between 60 and 79 years, as is shown in figure 5.1.

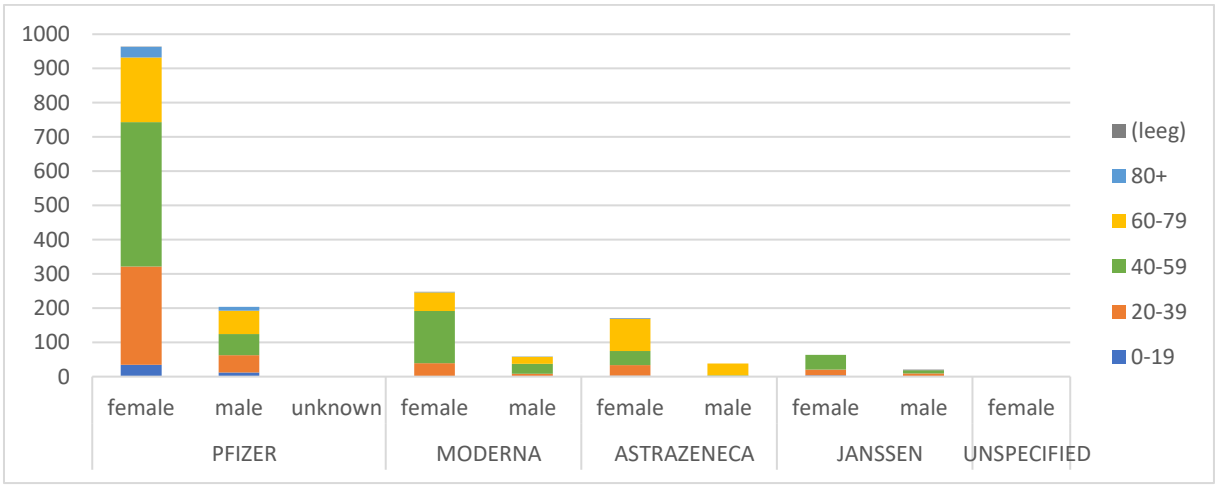

Figure 5.1: Distribution of the number of reports of angioedema with COVID-19 vaccines stratified per vaccine, sex and age group.

Time to onset and duration

The majority of the reactions of angioedema started within one day following vaccination. In 9.9% the reaction started within the first 15 minutes and 6.8% of the reactions in the next 15-30 minutes. The reports with latencies of more than a day, the time to onset varied from 1 day to 6 months, with a mean of 7.8 days. There were no specific patterns or eliciting factors in these reports.

In 412 (34.5%) of the cases that recovered, the duration of the reaction is known. The mean duration is 2.6 days, with a range of 5 minutes to 115 days. The mean 'minimal duration' in reports in which the outcome is not recovered/unknown, is 11.1 days with a range is 0-287 days. Chronic angio-oedema (more than 6 weeks) was reported in 33 reports (1.9% of total reports).

Treatment and outcome

In 675 (38.1%) of the reports, any kind of treatment was reported. Antihistamines were used by 472 (26.6%) people, systemic corticosteroids by 94 (5.3%), adrenalin by 34 (1.9%) and inhalation or nebulisation medication by 6 (0.3%). In 178 (10.0%) reports other types of treatments were also mentioned, such as analgesics (31; 1.7%), dermal corticosteroids (30; 1.7%), local cooling (24; 1.4%), antibiotics (17; 1.0%) and local oral therapies (15; 0.8%). One person was treated with C1-esterase inhibitor (Cinryze®) for treatment of an episode of already existing hereditary angioedema.

Recurrence

In 136 reports of angioedema following a second or third vaccination, swellings or other allergy like symptoms were reported with a previous COVID-19 vaccination. Those reports with two doses (n=106) had homologous vaccination schemes, except for two who had first Pfizer and second Moderna. Reports with three doses (n=30), 16 had heterologous vaccination schemes: pfizer-pfizer-moderna (n=9), moderna-moderna-pfizer (n=2), az-az-moderna (n=3), az-az-pfizer (n=2) and az-pfizer-moderna (n=1).

Allergy history

About one-third (31.9%) had any kind of allergy in their medical history. This concerns drug allergy (n=220; 12.4%) with NSAIDs and antibiotics reported most commonly, food allergy (n=156; 8.8%) for fruits, nuts, shellfish and many others, hay fever (n=124; 7.%), allergy to house dust mite or animals (n=75; 4.2%), insect sting allergy (n=33; 1.9%), asthma (n=32; 1.8%) and idiopathic/hereditary or unspecified types of angioedema (n=27; 1.5%) of which eight mentioned histamine intolerance. Four patients mentioned to have had an allergic reaction to another vaccine in the past: influenza (n=2), yellow fever (n=1) and travel vaccinations (n=1).

Other patient characteristics

A previous SARS-CoV-2 infection was reported in 265 (15.0%) of all cases. 226 (12.8%) patients were healthcare workers. Injections site reactions (inflammation, erythema, swelling, pruritus, pain) were reported in 469 (26.5%) cases .

Reporting rates

The reporting rates of angioedema following COVID-19 vaccination vary between vaccines and doses, as is shown in figure 5.2. Stratified for sex and age, the highest reporting rates were seen in women aged 20-39 with the 1st dose of AstraZeneca (RR 624.9 [CI 389.2-860.6] per million administered doses) and in men and women aged 40-59 with Janssen (RR respectively 252.5 [CI 184.5-320.4] and 460.9 [CI 323.1-598.6]) per million administered doses (not shown in the figure). The highest rates with mRNA vaccines are in women aged 40-59 years with 1st dose of Moderna (219.6 [CI 163.6-275.6]) and the 1st dose of Pfizer (RR 199.2 [CI 175.7-222.7]).

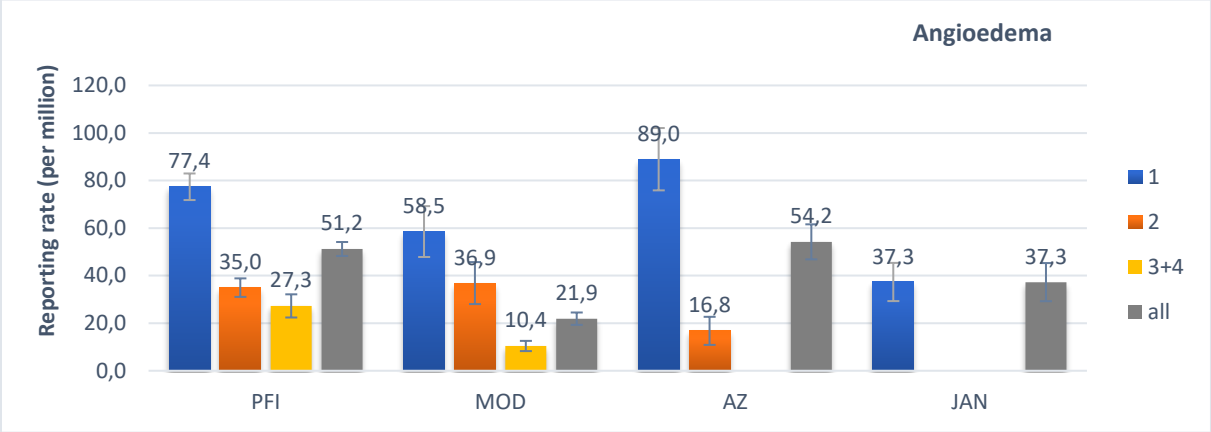

Figure 5.2: Reporting rates in number per million administered doses (95% CI) of angioedema (not part of anaphylaxis or allergic reaction) with COVID-19 vaccines, per dose and as total.

Discussion 'angioedema'

Due to the nature of spontaneous reporting and self-reported symptoms by patients, 'sensation of throat/tongue swelling' could not always be distinguished from objectified swelling or angioedema. This misclassification of symptoms may have caused an increase of reports of angioedema.

6. Urticaria

Until 23 May 2022, The Netherlands Pharmacovigilance Centre Lareb received 1429 spontaneous reports of urticaria that were *not part* of anaphylaxis or allergic reaction (as described above) following administration of COVID-19 vaccines, including 13 from marketing authorisation holders (MAH). To note, 74 reports reported to have had both urticaria and angioedema, which have been taken into account in both overview tables. Report and patient characteristics are summarized in table 6.1.

Table 6.1 Report and patient characteristics of reports of urticaria (not part of anaphylaxis or allergic reaction) following COVID-19 vaccines.

	Total	Pfizer	Moderna	Astra-Zeneca	Janssen	Unspecified vaccine
Reports (n)	1429	907 (63.5%)	269 (18.8%)	167 (11.7%)	81 (5.7%)	5 (0.3%)
- dose 1	772 (54.0%)	475 (52.4%)	82 (30.5%)	131 (78.4%)	81 (100%)	3 (60%)
- dose 2	466 (32.6%)	349 (38.5%)	80 (29.7%)	35 (21.0%)	0	2 (40%)
- dose 3	180 (12.6%)	81 (8.9%)	98 (36.4%)	1 (0.6%)	0	0
- dose 4	11 (0.8%)	2 (0.2%)	9 (3.3%)	0	0	0
Serious (n,% of all)	8 (0.6%)	5 (0.6%)	3 (1.1%)	0	0	0
- Other	8 (0.6%)	5 (0.6%)	3 (1.1%)	0	0	0
Reporter (n,%)						
- Healthcare prof.	135 (9.4%)	88 (9.7%)	16 (5.9%)	23 (13.8%)	7 (8.6%)	1 (20%)
- Consumer	1294 (90.6%)	819 (90.3%)	253 (94.1%)	144 (86.2%)	74 (91.4%)	4 (80%)
Sex and age						
- female (n,%)	1102 (77.1%)	704 (77.6%)	212 (78.8%)	127 (75.1%)	55 (67.9%)	4 (80%)
- male (n,%)	327 (22.9%)	203 (22.4%)	57 (21.2%)	40 (23.9%)	26 (32.1%)	1 (20%)
- Age (mean, range)	49.1 (8-95)	48.2 (8-93)	51.3 (20-95)	52.9 (18-81)	43.2 (19-65)	55.4 (29-79)
Time to onset (n,%)						

- < 15 minutes	35 (2.4%)	22 (2.4%)	8 (3.0%)	3 (1.8%)	2 (2.5%)	0
- 15-30 minutes	8 (0.6%)	5 (0.6%)	1 (0.4%)	2 (1.2%)	0	0
- < 1 day (> 30 min.)	606 (42.4%)	430 (47.4%)	98 (36.4%)	52 (31.1%)	23 (28.4%)	3 (60%)
- > 1 day	772 (54.0%)	444 (49.0%)	160 (59.5%)	110 (65.9%)	56 (69.1%)	2 (40%)
- Not exactly known	8 (0.6%)	6 (0.7%)	2 (0.7%)	0	0	0
Outcome						
- Recovered/ Recovering	738 (51.6%)	448 (49.4%)	146 (54.3%)	101 (60.5%)	41 (50.6%)	2 (40%)
- Not recovered/ unknown	691 (48.4%)	459 (50.6%)	123 (45.7%)	66 (39.5%)	40 (49.4%)	3 (60%)
Duration (mean, range)						
- If recovered (days)[#]	10.7 (0-183)	13.6 (0-183)	5.2 (0-35)	7.6 (0-56)	3.8 (0-21)	0
- If not recovered (days)[#]	22.1 (0-364)	21.8 (0-364)	18.5 (0-221)	31.6 (0-305)	22.2 (0-207)	6.7 (2-15)
- Duration > 6 weeks (n,%)	157 (11.0%)	107 (11.8%)	23 (8.6%)	20 (12.0%)	7 (8.6%)	0
Patient						
- Healthcare worker	193 (13.5%)	74 (8.2%)	46 (17.1%)	51 (30.5%)	20 (24.7%)	2 (40%)
- past COVID-19	212 (14.8%)	128 (14.1%)	43 (16.0%)	26 (15.6%)	15 (18.5%)	0
- Allergy history	471 (33.0%)	306 (33.7%)	99 (36.8%)	38 (22.8%)	27 (33.3%)	1 (20%)
- Injection site reaction	271 (19.0%)	160 (17.6%)	78 (21.1%)	25 (15.0%)	8 (9.9%)	0
- Recurrence (n,% dose)						
- - dose 2	101 (21.7%)	78 (22.3%)	17 (21.3%)	6 (17.1%)	0	0
- - dose 3	27 (15.0%)	14 (17.3%)	13 (13.3%)	0	0	0

[#] Duration if not recovered: reaction is ongoing at time of reporting, based on receive date minus start date, corrected for duration mentioned in case narrative. In 191 out of 738 reports (25.9%) the exact duration is known; in 637 out of 691 (53.1%) the '*at least ongoing at time of reporting duration*' was calculated based on provided data.

Reports

About half of the cases (54%) of urticaria were reported following the first dose and half with other doses. The majority (90.6%) has been reported by consumers themselves. Less than 1% was considered serious according to the CIOMS criteria, which is inherent to the condition.

Sex and age

In 1294 (77.1%) of the cases, the patient was female. The mean age for men and women was 51.3 years (range 12-84) and 48.4 years (range 8-95) respectively. The majority of men and women experiencing urticaria following COVID-19 immunisation were aged between 40 and 59 years, as is shown in figure 6. In total, there were 43 reports of urticaria concerning children (< 13; n=10) and adolescents (> 12; n=33).

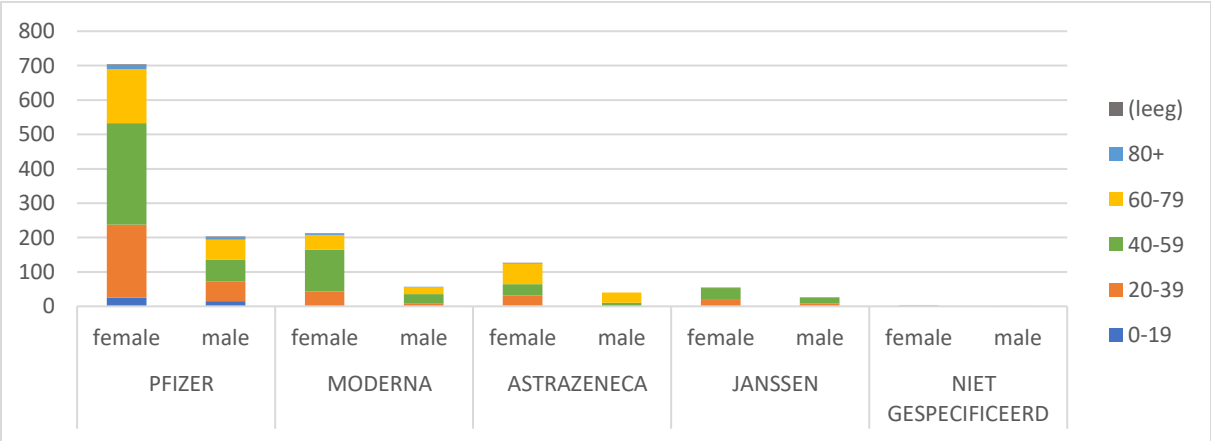

Figure 6.1: Distribution of the number of reports of urticaria with COVID-19 vaccines stratified per vaccine, sex and age group.

Time to onset

Time to onset was more than one day for the majority of the cases (54%) and 3% started within 30 minutes after vaccination. The mean time to onset in general for urticaria was 5.4 days (range 0-195 days). Figure X shows that the vast majority of the times to onset is less than one week after vaccination.

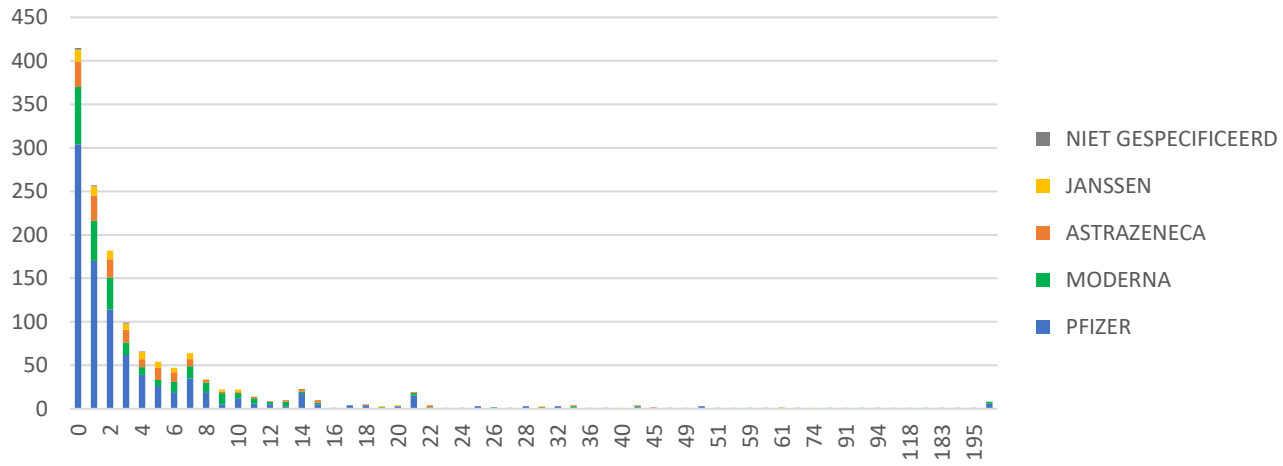

Figure 6.2. Times to onset (days) of reports (N) of urticaria following COVID-19 vaccination.

Treatment, outcome and duration

At time of reporting, about half of the patients recovered or was recovering from urticaria. In 191 (25.9%) of the cases that recovered, the duration of the reaction is known. The mean duration in these reports is 10.7 days, with a range of 5 minutes to 183 days. The mean 'minimal duration' in reports in which the outcome is not recovered/unknown, is 22.1 days with a range is 0-364 days. Chronic urticaria (more than 6 weeks) was reported in at least 157 reports (11.0% of total reports).

In 789 out of 1429 reports (55.2%) any kind of treatment was reported, such as antihistamines (n=632), cutaneous corticosteroids (n=138), systemic corticosteroids (n=84), adrenalin (n=3) and others (n=63) including antibiotics (n=9) and biologicals (omalizumab, n=8).

Recurrence

In 128 reports or urticaria following a second or third dose, allergic symptoms (urticaria or other) had also occurred with a previous dose. In reports with a recurrence following the second dose all except 4 had a homologous vaccination scheme; the exceptions were Jansen-Moderna, Jansen-Pfizer and two 'unspecified first vaccine'- Pfizer. Recurrence following a third dose apply to heterologous (n=13) and homologous (n=14) vaccination schemes and with the first, second or both doses (see table 6.2).

Table 6.2. Summary of vaccine sequences with recurrent urticaria or allergic symptoms following a third dose.

Moderna	**1st**	**2nd**	**both**	**Pfizer**	**1st**	**2nd**	**both**
Az-az-mod	1	2	2	**Az-az-pfi**	1		
Pfi-pfi-mod	2	4	1				
Mod-mod-mod		1		**Pfi-pfi-pfi**	2	4	7

Allergy history

One third of the patients reporting urticaria following COVID-19 vaccination mentioned any kind of allergy in their medical history. This concerns drug allergies (n=140), hay fever or pollen allergy (n=126), food allergies (n=92), urticaria (n=84), allergy to animals or house dust mite (n=66), insect sting allergy (n=25), asthma (n=22), angioedema (n=6), multiple allergies (n=18) and other/not

specified allergies (n=69). Among drug allergies, there were 6 reports with one or more previous allergic reactions to a vaccine (seasonal influenza (n=2), pandemic influenza H1N1 (n=2), pertussis, BMR and unspecified vaccine). Among 'other allergies', allergy to metals, formaldehydes, latex, household products, cosmetics and mast cell disease / histamine intolerance were mentioned a few times.

Other patient characteristics

There are no clear differences between vaccines in other patient characteristics such as being a healthcare professional, having had COVID-19 prior to vaccination or having had an injection site reaction as well. The relatively high percentage of healthcare workers with AstraZeneca can be explained by withdrawal of this vaccine from the campaign after a few months whereas healthcare professionals were vaccinated at first.

Reporting rates

The reporting rates of urticaria with COVID-19 vaccines vary between vaccines and doses, with the highest rate with AstraZeneca, as is shown in figure 6.3. Stratified for sex and age, highest reporting rates were seen in women aged 20-39 with 1st dose of AstraZeneca (RR 624.9 [CI 389.2-860.6] per million administered doses) and in women aged 40-59 with Janssen (RR 364.4 [CI 241.9-486.9] per million administered doses); not shown in the figure.

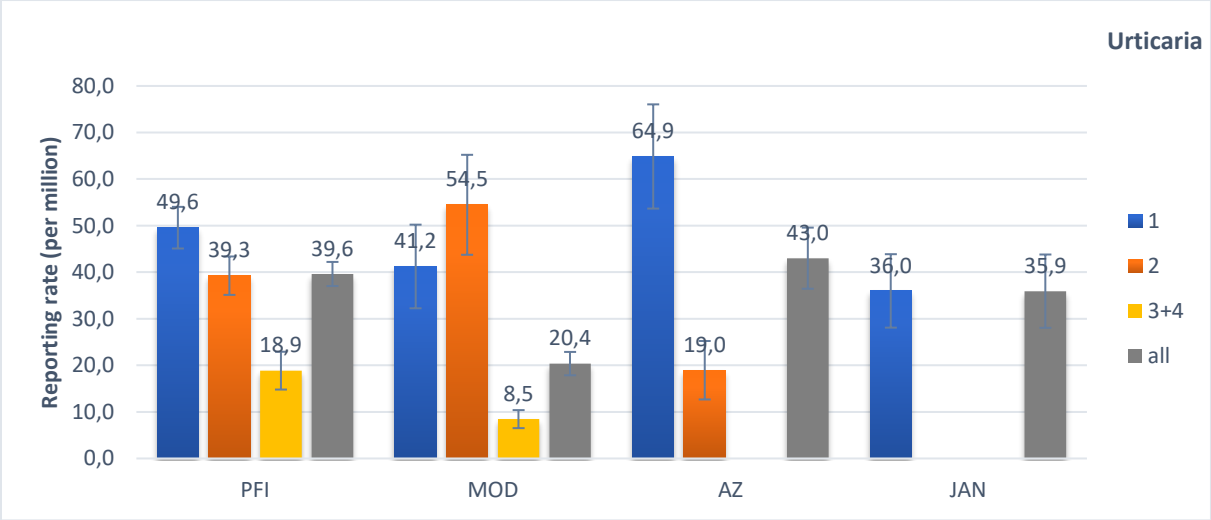

Figure 6.3: Reporting rates in number per million administered doses (95% CI) of urticaria (not part of anaphylaxis or allergic reaction) with COVID-19 vaccines, per dose and as total.

Discussion urticaria

The annual incidence of urticaria in general practitioners practices in The Netherlands is 6.5 per 1000 person-years, slightly more in women than men. The life-time prevalence of urticaria is estimated to be around 1.8%. Acute urticaria occur predominantly in young children (1-4 years), caused by viral infections and to a lesser extent by food, insect stings and vaccines [16]. In 30-40% of patients with urticaria also angioedema occurs and in 5-20% of patients the symptoms become chronic [17]. In the reports of urticaria following COVID-19 vaccination, 174 (5.2%) had co-occurrence with angioedema which is less than expected based on known epidemiology data [17]. Chronic urticaria (> 6 weeks) was reported in 11.0% of the cases which is comparable to known epidemiology data.

Drug-induced urticaria and angioedema have been reported by various (non-COVID) vaccines [18]. Urticaria following vaccination can be caused by either an allergic reaction or by the evoked immune response. Immune responses to vaccines and infections can exacerbate urticaria in people with chronic urticaria [16-17]. Several articles have been published on cutaneous reactions with COVID-19 vaccines, that mention non-acute and/or chronic urticaria [19-21].

In our reports, chronic or previous urticaria as medical history was mentioned in 84 out of 1429 (5.9%) cases. NSAID use is a common trigger of urticaria in people with chronic urticaria [22]. In 35 reports (2.4%) the use of NSAIDs is mentioned indicated for pain or fever following vaccination. However, we did not actively ask if people reporting urticaria had had urticaria or chronic urticaria before or used NSAIDs concomitantly.

Detailed background information was not available to calculate if more cases were observed than expected for (chronic) urticaria and angioedema.

7. Information from literature

Frequency of allergic reactions following vaccination

Luxi et al. recently reviewed the literature on allergic reactions to COVID-19 vaccines. Frequencies derived from reporting rates (based on spontaneous reporting) and cohort studies showed a high variability, due to differences in time, countries and definitions used for anaphylaxis and (severe) allergic reactions [23]. At the beginning of vaccination campaigns (January 2021), the CDC showed a reporting rate of 4.7 cases of anaphylaxis per million first doses for Comirnaty® and 2.5 for Spikevax® [7]. In September 2021, based on VAERS and V-safe, the reporting rates for anaphylaxis were 5.8, 5.1 and 9 per million doses for Comirnaty®, Spikevax® and Jcovden® respectively [24].

An Israelian cohort study (February 2021) found that 1.4% and 1.8% of people at risk for allergic reactions developed any allergic reaction with the first or second dose of Comirnaty® respectively; 0.7% developed anaphylaxis. An American prospective cohort study found a frequency of 2.0% of any allergic reaction following an mRNA vaccine, whereas the frequency of defined anaphylaxis was 0.02-0.03% with mRNA vaccines [25].

Until December 2021, from Eudravigilance and a rough estimate for administered vaccines in the European Union, reporting rates of anaphylaxis/anaphylactic shock were calculated: 3 per million doses for Comirnaty®, 2 per million for Spikevax®, 3 per million for Vaxzevria® and 2 per million for Janssen® [26].

Mechanism

The mechanism of hypersensitivity reactions to COVID-19 vaccines is not quite well understood. For the current COVID-19 vaccines, PEG (polyethylene glycol) in Comirnaty® and Spikevax® and the chemically related polysorbate in Vaxzevria® and Jcovden® have been suggested as potential triggering substances for hypersensitivity reactions [6]. Either as allergen for IgE-mediated allergy or as associated substance with CARPA (complement activation-related pseudo-allergy) [35]. However, the prevalence of IgE-mediated PEG allergy is extremely low and human data of CARPA as a mechanism to PEG is still inconclusive and specific tests are not available [27].

A true IgE-mediated reaction to vaccine components is difficult to demonstrate. In the study of Wolfson, patients with an allergic reaction to a first vaccine dose tolerated the second dose safely, regardless of the outcomes of skin prick test results to PEG and polysorbate [28]. Recurrence of the reaction with the next administration of the vaccine would be expected in the case of IgE-mediated allergy. However, recent studies show that recurrence of anaphylaxis or other severe allergic reactions is very rare with subsequent administrations supervised by allergists [29]. In a systematic review of 22 studies with 1366 patients with immediate allergic reactions to a first dose of a COVID-19 vaccine, 6 (0.16%) developed a severe allergic reaction following the second dose and 232 (13.6%) had mild symptoms [29].

For other mechanisms, either immune or non-immune mediated, no reliable tests are available in routine care.

8. Discussion

This overview describes the spontaneously reported reactions that can be seen with acute and/or type I allergic reactions with COVID-19 vaccines. In the Netherlands, a total of 3955 reports of symptoms possibly related to acute allergic conditions were received, concerning 90 reports of anaphylaxis, 298 reports of allergic reactions (not meeting anaphylaxis criteria), 1772 reports of angioedema and 1429 reports of urticaria following vaccine administration with COVID-19 vaccines. Another 366 reports describe aggravation of existing allergic conditions or new onset of certain allergies, after administration of a COVID-19 vaccine. This however does not automatically imply a causal relationship.

Report characteristics

The majority of the reports concern the first dose (60%) and there is a female predominance (> 80%). The mean age is about 40-50 years and there a few reports concerning children, adolescents or elderly.

Timing

Acute allergic reactions are expected to occur within 15-30 minutes. For anaphylaxis and other allergic reactions this was the case in two third and half of the reports, respectively. Note that in part of the reports 'within 1 day' was the reported latency which was not further specified. Late onset (> 24 hours) of angioedema and urticaria has also been reported in literature [21].

Outcome

The majority of patients with anaphylaxis or an acute severe allergic reaction was treated adequately and had recovered at time of reporting. There were no reports with a fatal outcome classified as anaphylaxis or allergic reaction. However, one person died following an asthmatic attack and three people died following reported angioedema although in none of these four reports an allergic cause of death has been confirmed and other causes could not be excluded.

Frequency

The reporting rates of *anaphylaxis* are quite similar to those found in literature, with 4.5 reports per million *first* doses for Comirnaty®, 7.6 per million for Spikevax®, 5.0 per million for Vaxzevria® and 1.3 per million for Jcovden®.

The Brighton Collaboration case definition criteria for anaphylaxis (appendix A) were used to classify cases of anaphylaxis with diagnostic certainty for comparison of frequencies in literature. However, these criteria were not always suitable for distinguishing true allergic anaphylaxis and misdiagnosis of vasovagal reaction or panic attack [30]. Only cases of anaphylaxis classified according to the Brighton Collaboration case definition, based on available information, were coded as such, and may have caused an underestimation of the number of true anaphylaxis cases.

The frequencies of other type I allergic reactions or symptoms (angioedema and urticaria) are less clear in literature, although frequencies up to 2% have been found in cohort studies [25]. In The Netherlands, type I like allergic reactions (not meeting anaphylaxis criteria) have reporting rates of 8-17 per million first doses. Reporting rates of single symptoms such as angioedema and urticaria were 37-89 per million first doses and 36-65 per million first doses, respectively.

Reporting rates were much lower with second and third or fourth doses. This can be explained that people at risk for allergic reactions and who had a severe and acute (< 4 hours) allergic reaction following any dose were discouraged to take the next regular dose. However, they were encouraged to contact allergists to evaluate whether the next dose could be administered with specialist supervision or to receive another vaccine brand. In spontaneous reporting, these next dose experiences have not been reported regularly. Studies in literature have shown that the vast majority of people with an allergic reaction to the first dose did not experience a severe reaction the next time [29]. Since it can be difficult to distinguish allergic symptoms from those related to stress, anxiety attack and vasovagal symptoms, the initial diagnosis following a first dose at the vaccination location

physician might have been different than the diagnose of specialist immunologists. The number of reports with recurrent allergic symptoms is quite low, as is also seen in literature.

Risk factors

A history of any kind of (self-reported) allergic condition was reported quite frequently: 71% in reports of anaphylaxis, 57% in reports of allergic reaction, 31% in reports of angioedema and 33% in reports of urticaria. This is also consistent with literature, in which a history of an allergic reaction up to 85% for vaccine induced anaphylaxis is recognized as a risk factor [23, 26, 34]. On the other hand, a small study of 68 people with severe atopic disease who had desensitisation therapies, none had a severe allergic reaction [32].

Aggravation of asthma, hay fever or other allergies following COVID-19 vaccination is poorly studied in literature. Only few cases of asthma exacerbation following COVID-19 vaccination have been published which is too little to support the association [33].

In 13% of the reports, the patient was a healthcare professional. How to report adverse drug reactions to Lareb as a pharmacovigilance centre may be better known by healthcare professionals than the general public. A SARS-CoV-2 infection prior to the reaction was reported in 14%. Being a health care professional or having had a prior COVID-19 infection do not seem to be risk factors for allergic symptoms following vaccination.

Injection site reactions were less reported with severe allergic and anaphylactic reactions than with angioedema and urticaria, probably because those were of less interest to mention. Injection site reactions are quite common and occur in > 10% of those being vaccinated [1-4], and are not associated with allergic symptoms.

Homologous or heterologous vaccine sequences

There are no clear patterns of increased risk with heterologous vaccination schemes. In reports with recurrent allergic symptoms, the vaccine sequences were mainly homologous (in basic series of first and second dose) or variably heterologous (with booster dose). In reports of allergic symptoms following a third or fourth dose (not particularly with recurrences), vaccine sequences were variably homologous or heterologous. As is shown in the tables above, the numbers of third dose reactions with the Moderna vaccine is relatively higher than the first and second dose and also compared to Pfizer third doses. This can be explained by the increased use of Moderna vaccines in the booster vaccination campaign and the relatively small use of Moderna vaccines during the basic vaccination campaign [5].

Reporting biases

This overview is based on spontaneous reports of suspected allergic reactions, which cannot be used to determine exact frequencies or to compare reactions between COVID-19 vaccines or with other vaccines. Several factors may have influenced reporting allergy related symptoms.

First, the novelty of the vaccines stimulates reporting of any suspected adverse event, mainly in the first period of the use. This is called the Weber effect, in which a peak of reports is seen within the first two years of newly authorised drugs. Second, a lot of media attention about the vaccination campaign and the worries about potential allergic reactions increases reporting of related symptoms as well. This is called notoriety bias, which is a selection bias that cases are more likely to be reported when there is known or likely cause for the event of interest [34]. Third, underreporting is a known feature of spontaneous reporting systems, since reporting is voluntary.

9. Conclusion

The reporting rates of anaphylaxis and other symptoms possibly related to severe acute allergic reactions with *first* doses of COVID-19 mRNA and vector vaccines is higher than the assumed rate of 1.3 per million immunisations in general, and are summarized in table 9.1. The reporting rates with COVID-19 vaccines in The Netherlands are quite similar to those mentioned in literature. The majority

of people with symptoms possibly related to acute allergic symptoms concern adult women with the first dose of any COVID-19 vaccine and two-thirds mentioned a medical history of any kind allergy. Relatively few reported a recurrence of allergic symptoms with more than one dose, which is consistent with other studies [29]. The mechanism of suspected hypersensitivity reactions to COVID-19 vaccines remains unclear. Because of the atypical pattern (predominantly first dose reactions and little chance of recurrence), other than IgE-mediated mechanisms or causes cannot be ruled out.

Table 9.1 Summary of reporting rates of anaphylaxis and allergic symptoms following COVID-19 vaccination. Reporting rates per million administered doses, with 95% CI, for the first dose (both men and women together) and for all doses in total.

	Anaphylaxis	Allergic reaction	Angioedema	Urticaria
Pfizer_1st dose	4.5 [3.2-5.9]	14.1 [11.7-16.5]	77.4 [71.8-83.0]	49.6 [45.1-54.0]
Moderna_1st dose	7.6 [3.8-11.5]	8.1 [4.2-12.1]	58.5 [47.8-69.2]	41.2 [32.3-50.2]
AstraZeneca_1st dose	5.0 [1.9- 8.1]	17.1 [11.3-22.8]	89.0 [75.9-102.1]	64.9 [53.7-76.0]
Janssen_1st dose	1.3 [0.0-2.9]	3.6 [1.1-6.1]	37.3 [29.3-45.4]	36.0 [28.1-43.9]
Pfizer_total	2.5 [1.9-3.2]	8.6 [7.4-9.8]	51.2 [48.3-54.1]	39.6 [37.0-42.2]
Moderna_total	1.2 [0.6-1.8]	3.9 [2.8-5.1]	21.9 [19.3-24.5]	20.4 [17.9-22.9]
AstraZeneca_total	2.6 [1.0-4.2]	10.2 [7.0-13.4]	54.2 [46.9-61.6]	43.0 [36.5-49.6]
Janssen_total	1.3 [0.0-2.9]	3.6 [1.1-6.1]	37.3 [29.3-45.3]	36.0 [28.1-43.9]

References

1. European Medicines Agency. SmPC Comirnaty. 2021. https://www.ema.europa.eu/en/documents/productinformation/comirnaty-epar-product-information_en.pdf Accessed 21-02-2022.
2. European Medicines Agency. SmPC Spikevax. 2021. https://www.ema.europa.eu/en/documents/productinformation/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf. Accessed 21-02-2022.
3. European Medicines Agency. SmPC Vaxzevria 2021. https://www.ema.europa.eu/en/documents/productinformation/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf Accessed 21-02-2022.
4. European Medicines Agency. SmPC Covid-19 vaccine Janssen. 2021. https://www.ema.europa.eu/en/documents/productinformation/covid-19-vaccine-janssen-epar-product-information_en.pdf. Accessed 21-02-2022.
5. Coronadashboard COVID-19-vaccinaties. Via: https://coronadashboard.rijksoverheid.nl/landelijk/vaccinaties (Access date: 29-6-2022)
6. Vrieze, de Jop. Suspicions grow that nanoparticles in Pfizer's COVID-19 vaccine trigger rare allergic reactions. Science, news, 21-12-2020. Via: https://www.science.org/content/article/suspicions-grow-nanoparticles-pfizer-s-covid-19-vaccine-trigger-rare-allergic-reactions
7. Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. JAMA. 2021 Feb 23;325(8):780-781. doi: 10.1001/jama.2021.0600. PMID: 33475702; PMCID: PMC8892260.
8. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018 Feb;141(2):463-472. doi: 10.1016/j.jaci.2017.12.971. PMID: 29413255; PMCID: PMC6602527.
9. RIVM. LCI Richtlijn COVID-19 vaccinatie. Via: https://lci.rivm.nl/richtlijnen/covid-19-vaccinatie#9-postvaccinale-verschijnselen (Version date: 14-6-2022; Access date: 29-6-2022)
10. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Sanchez Borges M, Senna G, Sheikh A, Tanno LK, Thong BY, Turner PJ, Worm M. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472. doi: 10.1016/j.waojou.2020.100472
11. Pichler WJ. Drug hypersensitivity reactions: classification and relationship to T-cell activation. In: Drug Hypersensitivity. Karger, 2007. Page: 171-172.
12. Jens U. Rüggeberg, Michael S. Gold, José-Maria Bayas, Michael D. Blum, Jan Bonhoeffer, et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine, Volume 25, Issue 31, 2007. https://www.sciencedirect.com/science/article/pii/S0264410X07002642?via%3Dihub
13. Prevalin. Pollenkalender. Via: https://www.hooikoorts.com/content/uploads/2019/04/Hooikoorts-Pollenkalender-2019.pdf (Version date 04-2019, Accessed at 25-7-2022)
14. NHG. Astma bij volwassenen. M27 (Version date July 2020). Via: https://richtlijnen.nhg.org/standaarden/astma-bij-volwassenen#volledige-tekst-epidemiologie
15. NHG. Allergische en niet allergische rhinitis. M48 (Version date January 2018). Via: https://richtlijnen.nhg.org/standaarden/allergische-en-niet-allergische-rinitis#volledige-tekst-epidemiologie
16. Ensina LF, Brandão LS, Neto HC, Ben-Shoshan M. Urticaria and angioedema in children and adolescents: diagnostic challenge. Allergol Immunopathol (Madr). 2022 May 17;50(S Pt 1):17-29. doi: 10.15586/aei.v50iSP1.538. PMID: 35726487.
17. AFE Verburg, Tj. Wiersma. NHG Behandelrichtlijn. Urticaria en angio-oedeem. Version date: June 2022 (accessed at 25-7-2022). Via: https://richtlijnen.nhg.org/behandelrichtlijnen/urticaria-en-angio-oedeem#volledige-tekst-epidemiologie
18. Tan SW, Tam YC, Pang SM. Cutaneous reactions to COVID-19 vaccines: A review. JAAD Int. 2022 Jun;7:178-186. doi: 10.1016/j.jdin.2022.01.011. Epub 2022 Feb 17. PMID: 35194586; PMCID: PMC8849859.
19. McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, Desai SR, French LE, Lim HW, Thiers BH, Hruza GJ, Blumenthal KG, Fox LP, Freeman EE. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. J Am Acad Dermatol. 2021 Jul;85(1):46-55. doi: 10.1016/j.jaad.2021.03.092. Epub 2021 Apr 7. PMID: 33838206; PMCID: PMC8024548.
20. Kroumpouzos G, Paroikaki ME, Yumeen S, Bhargava S, Mylonakis E. Cutaneous Complications of mRNA and AZD1222 COVID-19 Vaccines: A Worldwide Review. Microorganisms. 2022 Mar 15;10(3):624. doi: 10.3390/microorganisms10030624. PMID: 35336199; PMCID: PMC8953728.
21. Watts MM, Maurer LE, Grammer LC, Saltoun CA, Stevens WW. Delayed angioedema after administration of the severe acute respiratory syndrome coronavirus 2 messenger RNA vaccine. Ann Allergy Asthma Immunol. 2022 Feb;128(2):215-216. doi: 10.1016/j.anai.2021.10.021. Epub 2021 Oct 23. PMID: 34699970; PMCID: PMC8539818.

22. Cook KA, White AA. Chronic Urticaria with NSAID-Exacerbated Cutaneous Disease: A (NSAID) Challenge Worth Taking. J Allergy Clin Immunol Pract. 2020 Nov-Dec;8(10):3584-3585. doi: 10.1016/j.jaip.2020.07.043. PMID: 33161969. https://www.jaci-inpractice.org/article/S2213-2198(20)30801-1/fulltext
23. Luxi N, Giovanazzi A, Arcolaci A, Bonadonna P, Crivellaro MA, Cutroneo PM, Ferrajolo C, Furci F, Guidolin L, Moretti U, Olivieri E, Petrelli G, Zanoni G, Senna G, Trifirò G. Allergic Reactions to COVID-19 Vaccines: Risk Factors, Frequency, Mechanisms and Management. BioDrugs. 2022 Jun 13:1–16. doi: 10.1007/s40259-022-00536-8. Epub ahead of print. PMID: 35696066; PMCID: PMC9190452. https://link.springer.com/article/10.1007/s40259-022-00536-8
24. Rosenblum HG, Gee J, Liu R, Marquez PL, Zhang B, Strid P, et al. Safety of mRNA vaccines administered during the initial 6 months of the US COVID-19 vaccination programme: an observational study of reports to the Vaccine Adverse Event Reporting System and v-safe. Lancet Infect Dis. 2022;S1473–3099(22):00054–8. https://doi.org/10.1016/S1473-3099(22)00054-8.
25. Blumenthal KG, Robinson LB, Camargo CA, Shenoy ES, Banerji A, Landman AB, et al. Acute allergic reactions to mRNA COVID-19 vaccines. JAMA. 2021;325(15):1562–5. https://doi.org/10.1001/jama.2021.3976.
26. Sampath V, Rabinowitz G, Shah M, Jain S, Diamant Z, Jesenak M, Rabin R, Vieths S, Agache I, Akdis M, Barber D, Breiteneder H, Chinthrajah S, Chivato T, Collins W, Eiwegger T, Fast K, Fokkens W, O'Hehir RE, Ollert M, O'Mahony L, Palomares O, Pfaar O, Riggioni C, Shamji MH, Sokolowska M, Jose Torres M, Traidl-Hoffmann C, van Zelm M, Wang Y, Zhang L, Akdis CA, Nadeau KC. Vaccines and allergic reactions: The past, the current COVID-19 pandemic, and future perspectives. Allergy. 2021 Jun;76(6):1640-1660. doi: 10.1111/all.14840. Epub 2021 Jun 4. PMID: 33811364; PMCID: PMC8251022.
27. Paul J. Turner, Ignacio J. Ansotegui, Dianne E. Campbell, Victoria Cardona, Motohiro Ebisawa, et al. COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organization Journal, Volume 14, Issue 2, 2021. Via: https://www.sciencedirect.com/science/article/pii/S1939455121000119
28. Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X, Wickner P, Samarakoon U, Saff RR, Blumenthal KG, Banerji A. First-Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing. 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; PMCID: PMC8217699.
29. Chu DK, Abrams EM, Golden DBK, Blumenthal KG, Wolfson AR, Stone CA Jr, Krantz MS, Shaker M, Greenhawt M. Risk of Second Allergic Reaction to SARS-CoV-2 Vaccines: A Systematic Review and Meta-analysis. JAMA Intern Med. 2022 Apr 1;182(4):376-385. doi: 10.1001/jamainternmed.2021.8515. PMID: 35188528; PMCID: PMC8861900.
30. Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. Ann Allergy Asthma Immunol. 2021 Jul;127(1):133-134. doi: 10.1016/j.anai.2021.03.024. Epub 2021 Mar 27. PMID: 33781933; PMCID: PMC7997851.
31. Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, et al.. The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. J Allergy Clin Immunol Pract. 2021 Oct;9(10):3546-3567. doi: 10.1016/j.jaip.2021.06.006. Epub 2021 Jun 18. PMID: 34153517; PMCID: PMC8248554.
32. Dages KN, Pitlick MM, Joshi AY, Park MA. Risk of allergic reaction in patients with atopic disease and recent coronavirus disease 2019 vaccination. Ann Allergy Asthma Immunol. 2021 Aug;127(2):257-258. doi: 10.1016/j.anai.2021.04.024. Epub 2021 May 5. PMID: 33962029; PMCID: PMC8096529. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8096529/
33. Colaneri M, De Filippo M, Licari A, Marseglia A, Maiocchi L, Ricciardi A, Corsico A, Marseglia G, Mondelli MU, Bruno R. COVID vaccination and asthma exacerbation: might there be a link? Int J Infect Dis. 2021 Nov;112:243-246. doi: 10.1016/j.ijid.2021.09.026. Epub 2021 Sep 20. PMID: 34547487; PMCID: PMC8450144.
34. Neha R, Subeesh V, Beulah E, Gouri N, Maheswari E. Existence of Notoriety Bias in FDA Adverse Event Reporting System Database and Its Impact on Signal Strength. Hospital Pharmacy
35. Szebeni J, Storm G, Ljubimova JY, Castells M, Phillips EJ, Turjeman K, Barenholz Y, Crommelin DJA, Dobrovolskaia MA. Applying lessons learned from nanomedicines to understand rare hypersensitivity reactions to mRNA-based SARS-CoV-2 vaccines. Nat Nanotechnol. 2022 Apr;17(4):337-346. doi: 10.1038/s41565-022-01071-x. Epub 2022 Apr 7. PMID: 35393599.

This signal has been raised on October 12, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

Appendix A. Brighton Collaboration case definition of anaphylaxis [12]

For all levels of diagnostic certainty

Anaphylaxis is a clinical syndrome characterized by

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involving multiple (≥2) organ systems, as follows

Level 1 of diagnostic certainty

- ≥ major dermatological AND
- ≥ major cardiovascular AND/OR ≥ 1 major respiratory criterion

Level 2 of diagnostic certainty

- ≥ 1 major cardiovascular AND ≥ 1 major respiratory criterion
  OR
- ≥ major cardiovascular OR respiratory criterion AND
- ≥ minor criterion involving ≥ 1 different system (other than cardiovasc/resp)
  OR
- ≥ 1 major dermatologic AND ≥ 1 minor cardiovascular AND/OR minor respiratory criterion

Level 3 of diagnostic certainty

- ≥ 1 minor cardiovascular OR respiratory criterion AND
- ≥ 1 minor criterion form each of ≥ 2 different systems/categories

The case definition should be applied when there is no clear alternative diagnosis for the reported event to account for the combination of symptoms.

	Major criteria	**Minor criteria**
Dermatological or mucosal	• Generalised urticaria or generalised erythema • Angioedema, localized or generalized • Generalized pruritus with skin rash	• Generalised pruritus without skin rash • Generalized prickle sensation • Localized injection site urticaria • Red and itchy eyes

Cardiovascular	• measured hypotension
	• clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
	  ○ tachycardia
	  ○ capillary refill time >3 s
	  ○ reduced central pulse volume
	  ○ decreased level / loss of consciousness
		• Reduced peripheral circulation as indicated by the combination of at least 2 of:
		  ○ Tachycardia
		  ○ Capillary refill time > 3 sec without hypotension
		  ○ Decreased level of consciousness

Respiratory	• bilateral wheeze (bronchospasm)
	• stridor
	• upper airway swelling (lip, tongue, throat, uvula, larynx)
	• respiratory distress—2 or more of the following:
	  ○ tachypnoea
	  ○ increased use of accessory respiratory muscles
	  ○ recession
	  ○ cyanosis
	  ○ grunting
		• persistent dry cough
		• hoarse voice
		• difficulty breathing without wheeze or stridor
		• sensation of throat closure
		• sneezing, rhinorrhoea

Gastrointestinal		• diarrhoea • abdominal pain • nausea • vomiting
Laboratory		Mast cell tryptase elevation > upper normal limit