**Ascertainment bias in anaphylaxis safety data of COVID-19 vaccines**

**Abstract**

To determine rates of anaphylaxis to the first available COVID-19 vaccines, regulatory authorities are using a system, the Brighton Consortium Criteria, that is significantly overestimating the rate of anaphylaxis. Secondary analysis of the published data using scoring schemes widely in use by allergists, who see anaphylaxis on a frequent basis, shows significantly lower rates. This correction of ascertainment bias should reassure the public and regulatory authorities about the safety of the COVID-19 vaccines used to date.

Vaccination against COVID-19 began in the UK and USA in December 2020. In the UK, three initial reports of anaphylaxis resulted in a temporary embargo on the vaccination of those with a history of anaphylaxis.1 Initial US surveillance data reported an anaphylaxis rate of 11.1 cases per million doses for the Pfizer-BioNTech COVID-19 vaccine,2 and 2.5 cases per million doses for Moderna vaccine3 highlighting an apparently much higher reported occurrence of anaphylaxis into CDC passive vaccine surveillance systems, compared to historical data from existing vaccines, which typically is around 1.3 per million doses.4

The phenomenon of an initial “spike” in adverse event reporting which subsequently “settles” with time is common with safety reporting systems designed to be very sensitive to event detection. As the denominator (number of vaccines given) increases and additional information becomes available, case definitions are revised and reporting fatigue occurs. Indeed, the most recent data from the CDC, through 18 January 2021, now gives a rate of 5.0 cases (95%CI 3.7-6.6) per million doses for the Pfizer-BioNTech vaccine, and 2.8 cases (95%CI 1.7-4.2) for Moderna (5). Combined, the CDC reports a total of 71 anaphylactic reactions in 19,419,036 doses or 3.65 cases (95%CI (2.9-4.6) per million doses.5

As vaccine roll out accelerates, regulatory agencies must review safety decisions based on information generated from relatively small case numbers from the earliest stages, which have had significant consequences. It is imperative to hold analysis of all safety data to the highest standards. It is not uncommon for any adverse reaction occurring in association with a vaccination to be considered “allergic”, e.g. nausea or subjective oropharyngeal symptoms which are often psychogenic and difficult to refute on physical examination, in particular by non-allergy specialists who may lack robust experience in making such determinations. Vocal hoarseness can represent laryngeal oedema from an allergic reaction, but also vocal cord dysfunction, which can be anxiety related 6. Evidence from placebo-controlled allergen challenges shows that even urticaria can be stress-related. However, in contexts such as events associated with a new vaccine and vaccine technology, there is additional pressure to properly distinguish symptoms that are a direct result of mast cell degranulation (either directly or through IgE cross-linking of a known allergen) from other mechanisms of action, to discern true immune-mediated allergic reactions within the larger umbrella of adverse reactions.

To address this, the Brighton Collaboration case definition criteria were developed for the remote, post-hoc evaluation of vaccine-related adverse events7 The Brighton criteria are not used in clinical allergy or in non-vaccine-related research settings. More widely used clinical criteria for anaphylaxis - NIAID 20058 and WAO 20209 - do not have levels of “diagnostic certainty” used in the Brighton case definitions.(Table 1). On review of recently published data, a large proportion of the apparent anaphylaxis reactions reported to date by the CDC COVID-19 Vaccine Task Force 2,3 do not actually meet the Brighton case definition, despite classification as such (Table 2).Many (up to 71%) of the Brighton-defined anaphylactic reports for both the Pfizer-BioNTech and Moderna vaccines would not be classified as anaphylaxis (Table 2). If these more stringent criteria are also applied to the report by McNeill et al summarising reactions to non-COVID vaccinations reported to the US Vaccine Adverse Event Reporting System between 2009-11,5 far fewer cases (defined according to the Brighton criteria) have to be excluded. This is evidence that the Brighton criteria are open to overinterpretation and thus to ascertainment bias.

Anaphylaxis treatment guidelines advocate the early use of intramuscular epinephrine (epinephrine) to treat possible or likely anaphylaxis, but such epinephrine doses may be also administered “early” for only skin symptoms that might have resolved without progression to anaphylaxis. Also, actual usage of epinephrine varies highly in between physicians. Thus, epinephrine use (and resolution of symptoms) cannot be as a surrogate for a post-hoc diagnosis of anaphylaxis 10 and we are reassured that none of the Brighton, NIAID or WAO schemes does so.

Overestimation of the anaphylaxis rate to COVID-19 vaccines may delay or deter vaccination or cause undue referral for evaluation by immunologists or allergists and divert human and other resources to hospital-supervised vaccination. Public health bodies and healthcare professionals must apply appropriate criteria on the basis of sufficient clinical information to assign a diagnosis of anaphylaxis in the context of vaccine adverse event surveillance. The Pfizer-BioNTech vaccine currently appears to be associated with a 3-5-fold higher rate of anaphylaxis compared to the rate of anaphylaxis after non-COVID vaccines, but this rate is still very low and in contrast to other allergens used in immunotherapy, no anaphylaxis fatalities have been reported to date. This rate may even fall further with more data points.

As a medical community, we have a duty to ensure transparency and availability of reliable data to inform the public and policy, and to not risk contributing to vaccine hesitancy. Anaphylaxis, defined using the most rigorous criteria, is not much more common to the COVID-19 vaccines than other vaccines which have been used safely for more than 70 years and are widely accepted by the public. The variable national responses to COVID-19 showed rapid activation of public health measures was the most effective strategy. Now that vaccination is underway using new vaccines, the allergy community must reassure governments, public health bodies and vaccination programs to proceed with vaccination at the fastest possible pace.

Table 1 Comparison of Criteria for the Grading of Anaphylaxis

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| Brighton Collaboration Criteria 7 | NIAID Criteria (2005)8 | WAO Criteria (2020)9\* |
| 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 • ≥1 major dermatological AND • ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion Level 2 of diagnostic certainty • ≥1 major cardiovascular AND ≥1 major respiratory criterion OR • ≥1 major cardiovascular OR respiratory criterion AND • ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) 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 from each of ≥2 different systems/categoriesMajor criteria *Dermatologic or mucosal* • generalized urticaria (hives) or generalized erythema• angioedema\*, localized or generalized• generalized pruritus with skin rash*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 of consciousness or loss of consciousness*Respiratory* • bilateral wheeze (bronchospasm)• stridor• upper airway swelling (lip, tongue, throat, uvula, or larynx)• respiratory distress—2 or more of the following: • tachypnea • increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.) • recession • cyanosis • grunting\*Not hereditary angioedema.Minor criteria *Dermatologic or mucosal* • generalized pruritus without skin rash• generalized prickle sensation• localized injection site urticaria• red and itchy eyes*Cardiovascular* • reduced peripheral circulation as indicated by the combination of at least 2 of • tachycardia and • a capillary refill time of >3 s without hypotension • a decreased level of consciousness*Respiratory* • persistent dry cough• hoarse voice• difficulty breathing without wheeze or stridor• sensation of throat closure• sneezing, rhinorrhea*Gastrointestinal* • diarrhea• abdominal pain• nausea• vomiting*Laboratory* • Mast cell tryptase elevation > upper normal limit | Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, orboth (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)AND AT LEAST ONE OF THE FOLLOWINGa. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia (collapse], syncope,incontinence)2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient(minutes to several hours):a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BPb. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline | Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, orboth (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)AND AT LEAST ONE OF THE FOLLOWING:a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope,incontinence)c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting),especially after exposure to non-food allergens2. Acute onset of hypotension\* or bronchospasm or laryngeal involvement after exposure to a known orhighly probable allergen for that patient (minutes to several hours), even in the absence of typicalskin involvement.\*Criteria are co-endorsed by 50 global allergy societies, but not AAAAI or EAACI |

**TABLE 2.** Reported cases of anaphylaxis per million doses of COVID-19 vaccines in the literature, evaluated by independently by the authors and final consensus achieved.

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| **Anaphylaxis definition** | **Certainty** | CDC COVID-19 Vaccine Task Force | Non-COVID vaccines2009-2011, USA(Ref 4) |
|  | Pfizer-BioNTech14–23 Dec 2020(Ref 2) | Moderna21 Dec 2020–10 Jan 2021(Ref 3) |
| Brighton criteria (reported) | Level1-3 | 21 casesin 1, 893 360 doses11.1/million (95%CI 6.9-17.0)  | 10 casesin 4,041,396 doses 2.5/million  (95%CI 1.2-4.6) | 33 casesin 25,173,965 doses1.3/million (95%CI 0.9-1.8) |
| Brighton criteria (reassessed) | Level1-3 | 15 cases7.9/million (95%CI 4.4-13.1) | 5 cases1.2/ million (95%CI 0.4-2.9) | 31 cases1.2/million (95%CI 0.8-1.8) |
| National Institute of Allergy and Infectious Disease (NIAID) |  | 4 cases2.1 /million (95%CI 0.6-5.4) | 3 cases1.5/million (95%CI 0.2-2.2) | 18 cases0.7/million(95%CI 0.4-1.1) |
| World Allergy Organization (WAO) |  | 10 cases5.3/million (95%CI 2.5-9.7)  | 4 cases1.0/million (95%CI 0.3-2.5) | 25 cases1.0 /million(95%CI 0.6-1.5) |

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**Contributions**

JOBH and AB conceived the concept and developed it with all other authors. JH wrote all drafts with AB and all other authors contributed equally significantly to revisions. KB, PJT and MG performed the comparative analyses. All authors approved the final version.