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Perspective

We should abandon the Brighton Collaboration criteria for vaccine-associated anaphylaxis

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Background

The Brighton Collaboration criteria (BCC) were designed to provide standardized, globally accepted definitions for adverse events after immunization (AEFI).[1] The BCC for anaphylaxis combines minor and major criteria to assign a level of "diagnostic certainty" in the post hoc evaluation of vaccine surveillance data. These are not used outside vaccine surveillance settings, in which clinical criteria are more widely used. However, the global immunization effort against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has brought discussions regarding the definition and evaluation of vaccine-associated anaphylaxis to every health care setting.

Reporting Anaphylaxis During a Pandemic

The rapid development and rollout of SARS-CoV-2 vaccination programs were accompanied by an early peak in the reporting of AEFI, including anaphylaxis. Historically, pandemic and seasonal influenza vaccines are accompanied by the highest AEFI reporting rate because of the volume of cases being simultaneously immunized. As the vaccine rollout continues the early peak of BCC-defined reports of anaphylaxis after the SARS-CoV-2 vaccine has flattened, with an incidence of 7.91 cases per million vaccinations (n = 41,000,000 vaccinations; [95% confidence interval] 4.02-15.59) with no reported anaphylaxis-related fatalities.[2]

Vaccine-related anaphylaxis—a very rare event—generally must be identified and reported by those delivering vaccines through spontaneous or passive reporting. At the above anaphylaxis incidence rate, it would take a SARS-CoV-2 vaccinator 6 years to encounter a case (100 vaccinations/day x 200 working days/year). This contrasts starkly with a busy practicing allergist who may encounter anaphylaxis frequently in allergen immunotherapy or food challenges.

A marked limitation of the BCC for anaphylaxis is its dependence on the vaccinator to accurately interpret and record adequate information for later evaluation by an uninvolved third party. In comparison to more widely used clinical criteria, such as those outlined by the World Allergy Organization (WAO) and the National Institute of Allergy and Infectious Disease (NIAID), the BCC includes symptoms that may be nonallergic but misclassified as allergic because of subjective interpretation. Vasovagal episodes, paresthesia, isolated urticaria, or functional neurologic symptoms may be misclassified as symptoms that could support a BCC "cumulative" diagnosis of anaphylaxis. Immunization-related stress response poses a global burden to the extent that the World Health Organization has published guidance for health care providers. The BCC for anaphylaxis allows overinclusion and excessive reporting of all symptoms when the clinical diagnosis of anaphylaxis fundamentally requires very few. For all levels of certainty, using the BCC for anaphylaxis multiple (≥ 2) organ system involvements are required. The need for multisystem involvement does not account for patients who have anaphylaxis symptoms affecting 1 organ system. The simplified nature of the NIAID and WAO case definitions is not vulnerable to score-loaded cumulative combinations of major and minor criteria or on the use of different levels of clinical certainty. This is intended by NIAID and WAO to encourage rapid decision-making to minimize delay in epinephrine use in clinical settings. Many of the early reported cases of anaphylaxis to coronavirus disease 2019 (COVID-19) vaccines were not rapidly given epinephrine, in some way hinting that the diagnosis was only made retrospectively using the BCC, not prospectively, by a person familiar with the signs of evolving anaphylaxis. In addition to the accurate recognition of symptoms, the vaccinator must then record sufficient clinical detail of the event to allow post hoc classification. Underreporting and incomplete reporting are also well-recognized

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limitations of passive surveillance. Given this information, the case definition used for anaphylaxis as an AEFI should reflect the limitations of reporting by simplifying the criteria while maintaining sensitivity. The lower complexity of the NIAID and WAO case definitions would reduce the amount of information needed for passive reporting of suspected anaphylaxis. We suggest a simplified definition of anaphylaxis (eg, the NIAID or WAO definition) should be consistently used when assessing the risk of anaphylaxis in any setting, including adverse reactions to immunization, drugs, food (including oral immunotherapy), and venom.

Retrospective studies have compared the concordance of the BCC with other anaphylaxis definitions. A limitation in the direct comparison of these criteria is the necessitated exclusion of a likely allergen, a key aspect of the NIAID and World Health Organization systems from the BCC. Vaccines are very unlikely allergens for any recipient, and it is important that vaccination must not be assigned causality in the case definition for an AEFI. The first pathway of the NIAID definition does not require identification of a likely allergen and compares well to the BCC with moderate concordance.

We recently evaluated the accuracy of early reports of BCC-defined SARS-CoV-2 vaccine-related anaphylaxis, raising questions on the use of the BCC for anaphylaxis in the pandemic immunization setting.[3] Reported anaphylaxis cases were reevaluated using the NIAID and WAO clinical criteria. Up to 71% of BCC-defined anaphylaxis reports did not meet the NIAID or WAO criteria.[3] Application of the NIAID and WAO criteria to a previously published non−COVID-19 vaccine BCC-defined anaphylaxis cohort revealed only 58% who met the NIAID criteria and 81% who met the WAO criteria.[3] In a prospective active surveillance study of SARS-CoV-2 vaccination, 50% (7/14) of BCC anaphylaxis cases did not fulfill the NIAID criteria.[4] In health care workers, after SARS-CoV-2 vaccination, 25% of those meeting the BCC criteria did not meet the more stringent NIAID criteria.[5]

Accurate reporting of suspected AEFI including anaphylaxis is a cornerstone of vaccine safety and is especially important with new vaccines to allow the early detection of any safety concerns. However, overestimation and overreporting of AEFI, including anaphylaxis, are problematic, affecting public health strategy and public confidence. On an individual level, a diagnosis of possible anaphylaxis contraindicates revaccination with the same vaccine and affects the risk of vaccine-preventable disease. On a societal level, the overreporting of AEFI may fuel vaccine hesitancy or resistance. On a health care cost and resourcing level, the overestimation of anaphylaxis as an AEFI may result in a delay of vaccination, unnecessary referral to an allergist, or additional resourcing for supervised inpatient vaccination.

Conclusion

The clinical experience of using the BCC for the past 15 years, and especially in the setting of the COVID-19 pandemic, has highlighted new observations in the challenges and limitations of adopting a composite case definition, which depends on nonspecialists recognizing and reporting valid data for a very rare adverse event such as anaphylaxis. We recommend the adoption of the widely used clinical case definitions for anaphylaxis as a pragmatic alternative to the BCC, which better aligns the related fields of vaccinology and allergy.

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