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A Causality Assessment Framework for COVID-19 Vaccines and Adverse Events at the COVID-19 Vaccine Safety Research Center

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ABSTRACT

During the coronavirus disease 2019 (COVID-19) pandemic, conclusively evaluating possible associations between COVID-19 vaccines and potential adverse events was of critical importance. The National Academy of Medicine of Korea established the COVID-19 Vaccine Safety Research Center (CoVaSC) with support from the Korea Disease Control and Prevention Agency to investigate the scientific relationship between COVID-19 vaccines and suspected adverse events. Although determining whether the COVID-19 vaccine was responsible for any suspected adverse event necessitated a systematic approach, traditional causal inference theories, such as Hill's criteria, encountered certain limitations and criticisms. To facilitate a systematic and evidence-based evaluation, the United States Institute of Medicine, at the request of the Centers for Disease Control and Prevention, offered a detailed causality assessment framework in 2012, which was updated in the recent report by the National Academies of Sciences, Engineering, and Medicine (NASEM) in 2024. This framework, based on a weight-of-evidence approach, allows the independent evaluation of both epidemiological and mechanistic evidence, culminating in a comprehensive conclusion about causality. Epidemiological evidence derived from population studies is categorized into four levels—high, moderate, limited, or insufficient—while mechanistic

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evidence, primarily from biological and clinical studies in animals and individuals, is classified as strong, intermediate, weak, or lacking. The committee then synthesizes these two types of evidence to draw a conclusion about the causal relationship, which can be described as "convincingly supports" ("evidence established" in the 2024 NASEM report), "favors acceptance," "favors rejection," or "inadequate to accept or reject." The CoVaSC has established an independent committee to conduct causality assessments using the weight-of-evidence framework, specifically for evaluating the causality of adverse events associated with COVID-19 vaccines. The aim of this study is to provide an overview of the weight-of-evidence framework and to detail the considerations involved in its practical application in the CoVaSC.

Keywords: Causality; COVID-19 Vaccines; Adverse Events; National Academy of Medicine of Korea; COVID-19 Vaccine Safety Research Center

INTRODUCTION

The COVID-19 Vaccine Safety Research Committee (CoVaSC) of the National Academy of Medicine of Korea (NAMOK) was established on November 12, 2021, with the purpose of conducting scientific and systematic causality assessments between COVID-19 vaccines and adverse events (AEs).[1] Subsequently, on September 30, 2022, the COVID-19 Vaccine Safety Research Center was inaugurated and began operating under the auspices of CoVaSC. This center undertakes annual projects that involve reviewing both domestic and international literature related to AEs following COVID-19 vaccination and assessing causality based on established criteria. An independent causality assessment committee evaluates the relationships between vaccines and AEs and communicates its findings to the public, healthcare professionals, and the Korea Disease Control and Prevention Agency.

The assessment of causality typically proceeds through three stages. The first stage involves verifying a statistical association. If a statistically significant association is observed, it must be determined whether this association actually reflects a causal relationship. The second stage aims to ascertain true causality by ruling out non-causal explanations, such as bias, confounding, and interaction, in the conducted epidemiological study and its interpretation. Therefore, a systematic, evidence-based evaluation that employs rigorous epidemiological methods and comprehensive literature reviews is crucial to understanding the causality between AEs and vaccines. Finally, by using appropriate evaluation guidelines, the confirmed association can be considered scientific evidence, which allows for causal inferences.[2]

To understand vaccine adverse effects, it is essential to integrate epidemiological and mechanistic approaches. Both the United States Institute of Medicine (IOM) report in 2012 and National Academies of Sciences, Engineering, and Medicine (NASEM) report in 2024, based on the weight-of-evidence approach to vaccine adverse effects, underscore the importance of this collaborative effort.[3,4] These reports present a framework that categorizes the evidence from epidemiological and mechanistic studies into four levels, which are then synthesized to determine causality across one of four categories. The COVID-19 Vaccine Safety Research Center employs this framework to evaluate the causal links between COVID-19 vaccines and AEs. The objective of this study is to elucidate the causality assessment framework based on the weight-of-evidence approach and to describe the factors considered in its practical application in Korea.

CAUSALITY ASSESSMENT GUIDELINES

Causality refers to the relationship between two events, where one event is the direct cause of the other. However, the mere observation of AEs following vaccination does not conclusively establish the vaccine as the cause. While certain events may not occur without a preceding cause, a variety of factors can contribute to producing outcomes. In addition to vaccination, a number of underlying diseases or risk factors can lead to unexpected events, and individuals who appeared healthy at the time of vaccination may have had undetected health issues. Therefore, causality assessment guidelines are necessary to determine the causal relationship between vaccination and AEs.

These causality assessment guidelines include the Expert Committee of US Surgeon General criteria, the Bradford-Hill criteria, Howick's revision of Hill's guidelines for causation, and the modified Bradford-Hill Criteria proposed in the causality assessment manual for AEs following immunization (AEFIs). According to the WHO manual, causality assessment determines the likelihood of a causal relationship through a systematic evaluation of AEFI-related data (**Supplementary Table 1**).

In 1964, debates on the health impacts of smoking significantly advanced the methodologies for inferring causality based on epidemiological studies. The report by the Surgeon General's expert committee began applying evidence-based causality assessment by specifying criteria such as consistency, strength of association, specificity, temporality, and coherence.[5]

In 1965, Sir Austin Bradford Hill introduced the Bradford-Hill criteria for evaluating causality. These criteria systematically assess nine aspects of causal inference: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimentation, and analogy.[6] Hill argued that causality should be assessed based on the preponderance of evidence rather than any single criterion. While meeting these criteria can support causality, failing to meet some does not necessarily negate the causality itself. Thus, causality assessment in epidemiological research involves a series of judgments about the likelihood that observed associations in empirical data are causal.

Subsequently, Howick's revision and the WHO's 2019 causality assessment further refined this process. In 2009, Jeremy Howick's team at Oxford University simplified Hill's guidelines to make causality assessment more accessible. They proposed three main criteria—direct evidence, mechanistic evidence, and parallel evidence—by merging the biological gradient, strength of association, and temporality while excluding specificity.[7]

The World Health Organization (WHO) emphasizes the importance of distinguishing between AEs and adverse reactions before conducting causality assessments. Adverse reactions suggest a causal link, whereas AEs do not necessarily indicate a direct result of vaccination. Furthermore, the primary objective of assessing the causal relationship between vaccines and AEs is not to confirm or refute the connection between the event and the vaccination, but to evaluate the degree of certainty regarding such a potential association. Given the difficulties in establishing or rejecting a definitive causal relationship for a specific event, the WHO recommends conducting causality assessments at both individual and population levels.[8] This approach helps evaluate the probability of a causal relationship, with population-level assessments conducted through epidemiological studies.

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Among the studies evaluating the causality between COVID-19 vaccines and adverse effects during the COVID-19 pandemic, MacIntyre[9] applied the Bradford-Hill criteria, summarized all criteria for causation that are met (with consistency, specificity, temporality, and biological plausibility), and concluded that there is strong evidence supporting a causal connection between the COVID-19 vaccine (CHADOX1 NCOV-19 vaccine) and thrombotic syndrome.

Despite their widespread use, Hill's criteria for causality assessment have faced criticism early on, notably from prominent epidemiologists such as Rothman and Greenland.[10] Regarding the strength of association, which is one of Hill's criteria, it has been pointed out that even if recent epidemiological studies report results with a small magnitude of association, it is difficult to assert that there is no causal relationship. Regarding consistency, it appears natural for different results to be derived depending on the target population or research design, and thus the criterion of consistency is not always applicable. Given that many diseases can stem from the same factor, and one factor can be attributed to multiple diseases, specificity—meaning a one-to-one correspondence—is also challenging to employ as a criterion for determining causality.

WEIGHT-OF-EVIDENCE CAUSALITY ASSESSMENT FRAMEWORK

In 2012, the US IOM Committee to review AEs of vaccines, at the request of the Centers for Disease Control and Prevention, conducted the largest study of 158 vaccine-AE pairs to establish a scientific basis for determining whether eight different vaccines cause AEs, marking the first comprehensive review since 1994.[3] The summary reports stated that the importance of the dialogue between epidemiologic and mechanistic approaches cannot be overemphasized, where epidemiological studies evaluate general causation based on the statistical association between specific exposure factors (vaccination) and health outcomes (AEs) in a population, while the clinical evaluation of AE is based on a mechanistic understanding of reported cases.

The IOM's causality assessment framework involves conducting three evaluations. The initial evaluation focuses on the weight of evidence from the epidemiological literature, and the second evaluation concentrates on the weight of evidence from the mechanistic literature. Subsequently, the committee synthesizes the evidence gathered from both epidemiological and mechanistic studies and categorizes the collective body of evidence. This body of evidence informs the third evaluation, which seeks to ascertain the presence of a causal relationship.

In 2024, the National Academies of Sciences, Engineering, and Medicine (NASEM) released a report evaluating the causal relationship between COVID-19 vaccines and AEs.[4] The NASEM report follows the causal assessment process outlined in the IOM report, evaluating epidemiological and mechanistic evidence through a literature review and deriving comprehensive conclusions regarding causal relationships through independent committees. However, the individual assessment results for epidemiological and mechanistic evidence as described in the IOM report were not included; instead, the NASEM report only summarized descriptions of the reviewed literature and the final conclusions of causality assessment. The NASEM report evaluated 85 conclusions across 8 chapters regarding the causal relationships between COVID-19 vaccines and potential AEs. Among these, the report concluded that there is a confirmed causal relationship between the BNT162b2 (Pfizer-BioNTech) and mRNA-1273

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(Moderna) vaccines and myocarditis, while the evidence was deemed insufficient to confirm or refute a causal relationship between the Ad26.COV2.S (Johnson & Johnson) and NVX-CoV2373 (Novavax) vaccines and myocarditis.

The causality assessments in both the IOM and NASEM reports utilize a weight-of-evidence approach, based on a comprehensive literature review that includes both epidemiological and mechanistic studies.

Assessing the weight of epidemiological evidence

Epidemiological evidence is evaluated by reviewing peer-reviewed studies, which include both observational studies and randomized trials found within the scientific literature. Each study is assessed for methodological limitations and the precision of its findings. Methodological limitations can include a range of factors, such as inaccurate measurement of vaccine administration or AEs, inadequate control of confounding variables, incomplete or insufficient follow-up, and the lack of appropriate development and application of eligibility criteria. The precision of the findings is determined by examining the width of the 95% confidence interval for effect estimates, which reflects the statistical power to detect a significant increase in the risk of AEs. Studies that were identified as having very serious flaws were excluded from contributing to the evidence.

The committee evaluated both the quality and quantity of individual epidemiological studies, as well as the consistency of the overall body of studies in terms of the direction of effect. Central to this evaluation is the level of confidence the committee has in the closeness of the true effect to the average overall effect estimate obtained from the evidence. Key factors in assessing the weight of epidemiological studies are confidence, validity, precision, and consistency (**Table 1**).

Table 1. Assessments of the weight of epidemiological and mechanistic evidence

Category	Epidemiological evidence	Mechanistic evidence
Literature type	Epidemiological literature such as observational studies and randomized trials	Case reports or clinical and biological (human, animal, or in vitro studies) literature
Key elements of the assessment	· Confidence - The estimate of the average overall effect · Validity - The absence of confounding - Selection bias - Information or measurement bias (i.e., internal validity) - The generalizability (external validity) of the findings · Precision - The width of the confidence interval around an effect estimate · Consistency - Direction of effect	· Attribution elements - Specific details about the administered vaccine - Evidence of a clinician-diagnosed health outcome - A specified and reasonable time interval between vaccination and symptoms (i.e., temporality or latency) · Operative mechanism · Rechallenge cases · Laboratory-confirmed isolation of a vaccine strain virus in the patient
Categories of the weight of evidence assessment	· High: Two or more studies, each with negligible methodological limitations, consistently show the same direction of effect, providing high confidence · Moderate: A single study with negligible methodological limitations or a collection of studies generally showing consistent effects, providing a moderate level of confidence · Limited: A single study or a collection of studies lacking precision or consistency, resulting in limited or low confidence · Insufficient: No epidemiological studies of sufficient quality	· Strong: At least one case in the literature concludes that the vaccine was a contributing cause of the adverse event, based on an overall assessment of available cases and clinical, diagnostic, or experimental evidence aligning with relevant biological responses to the vaccine · Intermediate: At least two cases conclude that the vaccine may be a contributing cause of the adverse event · Weak: There is insufficient evidence from cases in the literature to conclude that the vaccine may be a contributing cause of the adverse event · Lacking: No clinical, diagnostic, or experimental evidence aligns with relevant biological response to the vaccine, regardless of individual cases mentioned in the literature

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The assessment of the weight of the epidemiological evidence was classified into four levels: high, moderate, limited, and insufficient. A high level indicates a strong degree of confidence, supported by two or more studies with minimal methodological limitations that demonstrate a consistent direction of effects. A moderate level suggests either a single study with minimal methodological limitations or multiple studies that generally show consistent effects, yielding a moderate degree of confidence. Limited applies to either a single study or a group of studies that suffer from a lack of precision or consistency, leading to low confidence in the findings. Insufficient is used when there are no epidemiological studies of adequate quality available. Evidence classified as high or moderate specifies the direction of effect, which may indicate an increased risk of AEs, a decreased risk, or no change in risk (null). In contrast, assessments labeled as limited or insufficient do not specify a direction of effect.

Assessing the weight of mechanistic evidence

The mechanism by which a vaccine might trigger a specific AE is determined through the identification and evaluation of clinical and biological evidence. Initially, the committee reviewed peer-reviewed literature to assess whether there was evidence to suggest a causal relationship between a vaccine and an AE. This involved considering case reports or clinical studies that documented such events occurring within a reasonable time frame after vaccination. Following this initial review, the committee looked for additional information from clinical and biological sources, including human, animal, or in vitro studies, that could provide evidence of a pathophysiological process or mechanism that could plausibly cause the AE in response to a particular vaccine.

The committee evaluated each case report using a well-established set of criteria known as attribution elements (**Table 1**). At a minimum, for a case to contribute to the weight of evidence assessment, it had to specifically mention the administered vaccine, provide evidence of a clinician-diagnosed health outcome, and demonstrate a reasonable time interval between vaccination and the onset of symptoms. Mechanistic weight of evidence assessments excluded case descriptions that lacked these three essential attribution elements. Upon confirming cases with the requisite attribution elements, the committee then assessed the weight of evidence based on the presence of evidence supporting a possible operative mechanism, as found in clinical or biological literature, that substantiates the association between vaccination and AEs. Cases of rechallenge, where an AE recurs after multiple doses of a specific vaccine in the same individual, could strengthen the weight of the evidence. Additional compelling evidence in the case description may include the laboratory-confirmed isolation of a vaccine strain virus in the patient. Evidence from animal studies was also considered informative if the disease model (adverse outcome) was well-established as relevant to human conditions, or if there was a thorough understanding of the basic immunology underlying the vaccine reaction.

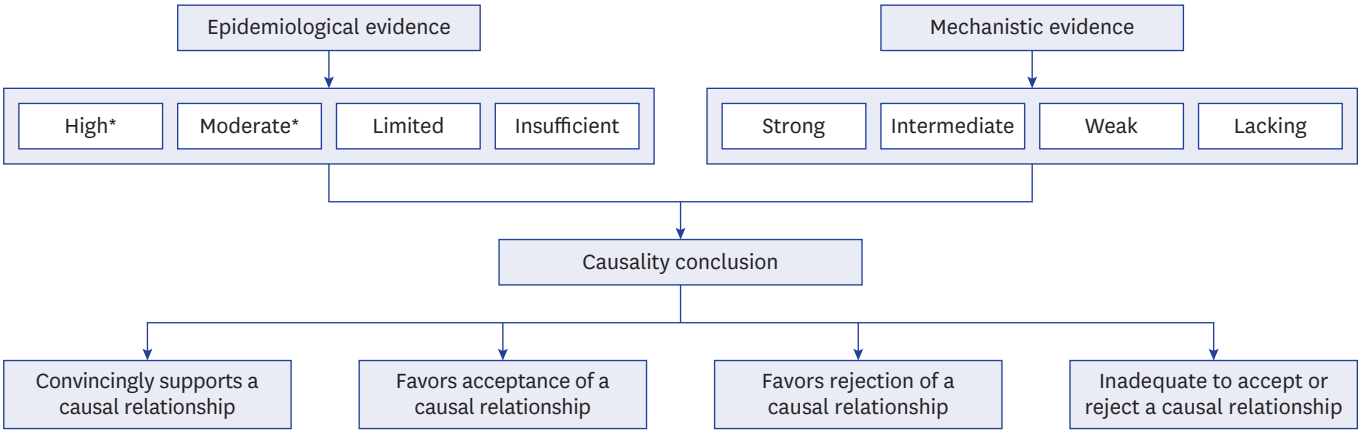
The assessment of the weight of mechanistic evidence was categorized into four distinct levels: strong, intermediate, weak, or lacking. The term “strong” is used when there is at least one documented case in the literature that supports the conclusion that the vaccine was a contributing factor to the AE. This conclusion is based on a comprehensive evaluation of available cases and clinical, diagnostic, or experimental evidence that is consistent with the biological responses to the vaccine. “Intermediate” is applied when there are at least two cases suggesting that the vaccine may have contributed to the AE. In some instances, the committee may find the evidence insufficient to assert that the vaccine could be the cause, even with a minimum of two cases; this is then classified as low-intermediate. The

designation "weak" is given when the evidence in the literature is deemed inadequate to support the conclusion that the vaccine may be the cause of the AE. Finally, "lacking" is used when there is an absence of clinical, diagnostic, or experimental evidence that corresponds with the relevant biological responses to the vaccine, regardless of individual cases cited in the literature.

Assessing the final causality conclusion

The committee initiated its assessment from a neutral perspective, avoiding any presumption of causation or absence thereof until all the evidence had been thoroughly examined. The committee maintained this neutral approach unless the combined epidemiological and mechanistic evidence warranted a more definitive statement regarding causation, indicating either an increased or decreased risk of AEs associated with vaccines. The focus of this framework was to determine whether the vaccine causes AEs, rather than evaluating the vaccine's effectiveness. The committee developed a framework for reaching a final conclusion on causality, as depicted in **Fig. 1**. It is important to recognize that mechanistic evidence can only support the presence of causation, whereas epidemiological evidence can support either a causal relationship or the absence of one within the general population.

The committee classified causality conclusions into four categories. The term "evidence convincingly supports a causal relationship" is reserved for situations where there is compelling evidence of a definitive relationship. A conclusion of "convincingly supports" (evidence established in the NASEM report) is made when there is strong epidemiological evidence from at least two rigorously conducted studies showing an increased risk, or when there is robust mechanistic evidence from at least one case report that provides persuasive support for the vaccine causing the AE. The phrase "evidence favors acceptance of a causal relationship" indicates that the evidence is strong and generally suggestive, but not yet conclusive or definitive. The designation "favors acceptance" is used when there is moderate epidemiological evidence of an increased risk or intermediate mechanistic evidence. Conversely, the phrase "evidence favors rejection of a causal relationship" conveys that there is strong and generally convincing evidence against a causal link. A conclusion labeled as "favors rejection" is reached when there is high or moderate epidemiological evidence indicating no effect or a reduced risk, and in the absence of strong or intermediate mechanistic evidence supporting a causal relationship. Lastly, the phrase "evidence is



*This word refer to adverse event risk, presenting 3 possibilities: an increase in risk, a decrease in risk, or no change in risk

Fig. 1. Causality assessment process. This figure has been drawn, referencing the Institute of Medicine's causal assessment framework.

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inadequate to accept or reject a causal relationship" refers to situations where the evidence is insufficient to either confirm or refute a causal relationship. This may include cases with sporadic, conflicting, or low-quality evidence, or evidence that is merely suggestive. A conclusion described as "inadequate to accept or reject" is made when the reliability of epidemiological evidence is limited or insufficient, and the mechanistic evidence is weak or absent. This category also applies when there is a moderate certainty that epidemiological evidence shows no effect, yet there is intermediate mechanistic evidence.

THE APPLICATION OF THE IOM'S CAUSALITY ASSESSMENT FRAMEWORK AT THE COVID-19 VACCINE SAFETY RESEARCH CENTER

Over the past few years, the COVID-19 Vaccine Safety Research Center of NAMOK has conducted causality assessments to determine the relationship between COVID-19 vaccines and AEs. In the first year of research, the causality assessment process utilized both the Bradford-Hill criteria and the US Surgeon General's criteria. An ad-hoc committee compiled and reviewed analysis results and evidence from both Korean and international sources. Following a discussion among the committee members, a final decision was reached on whether the cases met the causality criteria.[1] Since entering its second year, the COVID-19 Vaccine Safety Research Center has adopted the causality assessment framework established by the US IOM (**Table 2**). The center evaluates causality by examining whether study findings are consistent with existing epidemiological literature and determining the plausibility or feasibility of mechanistic explanations. The results are shared with healthcare professionals and the general public through regular forums, reports, and briefings.

The COVID-19 Vaccine Safety Research Center established an independent committee to conduct causality assessments. Two examples of AEs evaluated using this framework are as follows (**Supplementary Table 2**). For the relationship between COVID-19 vaccination and acute transverse myelitis (ATM), the mechanistic assessment was rated as "intermediate." This was based on multiple reports of ATM following COVID-19 vaccination and a disproportionality analysis using the WHO pharmacovigilance database, VigiBase, which showed higher reporting of ATM post-COVID-19 vaccination compared to other vaccines. The epidemiological assessment was based on large-scale database studies conducted in Europe and South Korea. A self-controlled case series (SCCS) study using United Kingdom insurance claim data suggested an increased risk of ATM post-vaccination, although it was not statistically significant. Conversely, an SCCS study using Korean insurance claim

Table 2. Causality assessment tool of the COVID-19 Vaccine Safety Research Center

Division	Assessment results					
Mechanistic assessment	Strong Comment:	Intermediate	Low intermediate	Weak	Lacking	
Epidemiological assessment	High (increased risk) Comment:	High (decreased risk or no effect)	Moderate (increased risk)	Moderate (decreased risk or no effect)	Limited	Insufficient
Causality assessment	(CS) Evidence convincingly supports a causal relationship (evidence established) (FA) Evidence favors acceptance of a causal relationship (I) Evidence is inadequate to accept or reject a causal relationship (FR) Evidence favors rejection of a causal relationship Comment:					

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data observed a statistically significant risk. Combining these results, the epidemiological assessment was rated as "moderate (increased risk)." Comprehensively considering the existing literature, the evidence was deemed to "favor acceptance" of a connection between COVID-19 vaccination and ATM. This evaluation applies to all COVID-19 vaccines irrespective of type. Based on these CoVaSC findings, in February 2023, the BNT162b2 and mRNA-1273 vaccines were recognized for their association with suspected ATM, leading to government compensation for ATM cases following mRNA vaccination. In contrast, the mechanistic assessment for COVID-19 vaccines and multiple sclerosis (MS) was rated as "lacking." Repeatedly consistent findings from previous studies indicated no association between COVID-19 vaccines and MS. The epidemiological assessment was rated as "insufficient" because it was difficult to verify the cases, except for the investigations conducted by CoVaSC, and most studies failed to show statistical significance. Considering the CoVaSC study results and the comprehensive evaluation of the existing literature, the evidence was deemed "inadequate to accept or reject" a connection between COVID-19 vaccination and MS.

DISCUSSION AND CONCLUSION

Assessing the causality of the observed increase in AEs following vaccination requires careful consideration of both population-based epidemiological studies and mechanistic research. Ideally, to determine whether a specific exposure factor causes a health outcome, one would need to observe the same individuals in both exposed and unexposed scenarios simultaneously. However, this approach is not practical in real-world settings. Therefore, when interpreting associations from epidemiological studies as causal, it is crucial to ensure that the observed association is not the result of various biases or mere chance, and to evaluate whether it meets established criteria for making causal inferences. Furthermore, establishing a direct causal link between a specific AE and a vaccine based solely on individual case reports is typically rare and fraught with challenges. Therefore, a systematic review that encompasses both epidemiological and mechanistic studies is essential to determine whether the vaccine is the cause, not the cause, or if the relationship remains uncertain. It is important to remember that causality is an interpretation, not a concrete entity. The criteria used in assessing causality should be viewed as tools to aid in the judgment of causality, rather than as definitive arbiters of reality.

The practical application of the weight-of-evidence causality assessment framework presented several challenges. These included ensuring the quality of data and establishing a clear cause-and-effect relationship amidst complex factors. Applying consistent criteria when reviewing individual articles and assessing evidence proved difficult. Furthermore, reaching conclusions about causality often required extensive discussion and debate, incorporating expert clinical and scientific judgment. There were also limitations in assessing epidemiological causal relationships using vaccination data and claims records that covered the entire South Korean population. For instance, there could be instances of over-reporting, where patients are given a clinical diagnosis without actually having the AE. This could skew the data and compromise the accuracy of the evaluation. Therefore, it is necessary to confirm the diagnostic validity and appropriateness of suspected adverse cases by integrating them with medical records, which would lead to the generation of higher-quality evidence. Additionally, when dealing with extremely rare AEs, it can be difficult to achieve statistical significance using epidemiological study designs alone. Therefore, a supplementary review process for individual adverse cases is required. Finally, a limitation

of the causality assessment of COVID-19 vaccines and AEs conducted in Korea is the absence of causality assessments for each vaccine platform. In future research, causality assessments should be conducted individually for each COVID-19 vaccine platform and AE case.

In South Korea, the Korean algorithm for causality assessment of adverse drug reactions was established in 2002 and has since been updated to version 2.0.[11] This version evaluates causality by considering various factors, including temporal relationships, the impact of dose reduction or discontinuation, the patient's history of AEs, concomitant drug use, potential non-drug causes, available medication information, details of re-dosing, and results from specific tests. Each factor is scored, and the cumulative score determines the causality level, which is categorized as certain, probable, possible, or unlikely. Although the algorithm is comprehensive, it may pose difficulties for inexperienced evaluators due to its complexity.[12] Additionally, the reliance on subjective judgment can make evaluations challenging. This is particularly true when assessing patients with underlying conditions who are taking multiple medications. The absence of specialized diagnostic tests and ethical concerns about re-dosing for assessment purposes further add to the complexity. Therefore, it is necessary to develop a Korean causality assessment algorithm that incorporates both epidemiological and mechanistic approaches. Establishing accurate evaluation criteria and subdivisions is crucial, which calls for the creation of specific criteria and guidelines for the weighting process. If a Korean algorithm tailored to local conditions is developed, used, and refined, it could serve as an effective initial method for causality assessment and contribute to the evaluation of vaccine safety within the country's healthcare system.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Comparison of causality assessment criteria

Supplementary Table 2

Cases of application of the causality assessment framework for COVID-19 vaccines and adverse events

REFERENCES

1. Jeong NY, Park H, Oh S, Jung SE, Kim DH, Shin HS, et al. A framework for nationwide COVID-19 vaccine safety research in the Republic of Korea: the COVID-19 Vaccine Safety Research Committee. *Osong Public Health Res Perspect* 2023;14(1):5-14. PUBMED | CROSSREF
2. Maldonado G, Cox LA. Causal reasoning in epidemiology: philosophy and logic. *Glob Epidemiol* 2020;2:100020. CROSSREF
3. Institute of Medicine. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, D.C., USA: The National Academies Press; 2012.

4. National Academies of Sciences, Engineering, and Medicine. *Evidence Review of the Adverse Effects of COVID-19 Vaccination and Intramuscular Vaccine Administration*. Washington, D.C.: National Academies of Sciences, Engineering, and Medicine; 2024.
5. United States Surgeon General's Advisory Committee on Smoking. *Summary of the Report of the Surgeon General's Advisory Committee on Smoking and Health*. Washington, D.C., USA: US Department of Health, Education, and Welfare, Public Health Service; 1964.
6. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58(5):295-300. PUBMED | CROSSREF
7. Howick J, Glasziou P, Aronson JK. The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? *J R Soc Med* 2009;102(5):186-94. PUBMED | CROSSREF
8. World Health Organization. *Causality Assessment of an Adverse Event Following Immunization (AEFI): User Manual for the Revised WHO Classification Second Edition, 2019 Update*. Geneva, Switzerland: World Health Organization; 2019.
9. MacIntyre CR. Using the Bradford-Hill criteria to assess causality in the association between CHADOX1 NCOV-19 vaccine and prothrombotic immune thrombocytopenia. *Glob Biosecur* 2021;3(1).
10. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia, PA, USA: Lippincott-Raven Publishers; 1998.
11. Hong KS, Park BJ, Shin SG, Yang JS, Lee SM, Kim Y, et al. Development of Korean algorithm for causality assessment of adverse drug reactions. *J Korean Soc Clin Pharmacol Ther* 2002;10(2):129-42. CROSSREF
12. Kim BR, Lee JS, Han OY, Jeong SH, Yim HW, Jung KE, et al. Comparison between WHO-UMC causality categories and Korean algorithm version 2.0 for causality evaluation of adverse drug reactions. *J Pharmacoepidemiol Risk Manag* 2012;5(1):31-9.