ESC HEART FAILURE
ESC Heart Failure 2024; **11**: 2467–2468
Published online 25 April 2024 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14819

Letter to the editor regarding 'Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis'

Vaccination is a well-proven public health intervention. Since the latter half of the 20th century, vaccination policies have been increasingly informed by peer-reviewed publications. Given this, Hulscher et al.[1] may have major implications on the public's health and perception of COVID-19 vaccination. However, we believe the conclusions drawn by the authors fail to match the methodologies used. Therefore, caution should be exercised by readers when drawing conclusions from the study findings.

The individual-level causal effects of COVID-19 vaccination on myocarditis deaths were poorly established in the selected autopsy cases. First, information on relevant covariates was limited. Covariates recorded in Table 1 included sex, age, vaccine dose number, time between vaccination and myocarditis, vaccine brand, and autopsy notes.[1] However, important variables that may be associated with myocarditis death including non-cardiac comorbidities and exposure to other vaccinations or medications were missing. In addition, the implications of the included demographic information were never discussed. Previous research shows that COVID-19 vaccination was associated with risk of myocarditis only in those younger than 40.[2] Of the 28 cases, 14 were older than 40 years of age. These cases were attributed to COVID-19 vaccination, contrary to prior evidence, and require a higher burden of proof of causality, which was not provided by the authors. Furthermore, the temporality of the association was poorly established in some cases. Five myocarditis deaths occurred fewer than 2 days after vaccination. While vaccination may have occurred before myocarditis death, the date of initial myocarditis signs and symptoms was never reported. In the five cases where times to death after vaccination were so short, it is biologically improbable that vaccination occurred before the onset of myocarditis due to the time needed to mount an immune response to vaccine antigens and result in myocarditis. Finally, coincidental causes of death from myocarditis cannot be ruled out given the information provided. Comorbidities contributing to death from myocarditis include genetically programmed disease, drug or toxin exposure over an acceptable level, and even non-measured infections present before or at the time of immunization.[3] Hulscher et al. failed to address any potential comorbidities, and instead used the existence of these cases as a reason for '… establish[ing] that all 28 deaths were most likely causally linked to COVID-19 vaccination by independent review of the clinical information presented in each paper'.[1] In some of the cited autopsy case reports, even the authors themselves stated that individual-level causal inference cannot be made based on their findings. For example, in their case commentary, Verma[4] found an association between COVID-19 vaccination and fulminant myocarditis. However, the case report only included a sample of two individuals where comorbidities were not assessed and PCR testing was reported only for COVID-19. In their own discussion section, Verma[4] concluded that no direct causal relationship could be established.

To further support their hypothesis of a causal relationship between COVID-19 vaccination and death from myocarditis, Hulscher et al. invoked the Bradford Hill criteria. However, it should be noted that rather than serving as a definitive checklist to determine causality, the Bradford Hill criteria are intended to provide a framework of considerations for constructing epidemiological assessments of causality.[5] In this application, the World Health Organization (WHO) criteria for establishing causality between vaccination and an adverse event[3] is widely accepted. The WHO criteria require consideration of temporality, alternative explanations, proof of association, prior evidence, biological plausibility, and population-based evidence, to conclude a causal association. While some of these criteria may be met, the greatest missing component in Hulscher et al. was population-based evidence, which cannot be assessed from a series of autopsies. In the absence of such evidence, the association between the COVID-19 vaccine and death from myocarditis would fall into either the 'indeterminate' or 'inconsistent with causal association' categories. In fact, a study that conducted a population-level assessment of the association between the COVID-19 vaccine and myocarditis found no excess risk of myocarditis in vaccinated groups.[2]

In addition, we identified many inconsistencies where Hulscher et al.[1] misrepresented referenced papers in various forms. For example, the authors opened the Discussion section with an assertion that their findings of a causal link between the COVID-19 vaccine and death from myocarditis were consistent with the available epidemiological literature on their topic, referencing 994 papers retrieved from PubMed through a keyword search with the terms ('myocar-

ditis' AND 'COVID-19 vaccination'). A keyword search alone is not sufficient to conclude that each of these articles are in agreement with the existence of this causal relationship nor that they investigated that specific association. Furthermore, there are several instances where cited papers were retracted or not peer-reviewed. In one example, Skidmore[3] was marked with an editor's note regarding unsubstantiated claims on 26 January 2023, resulting in a retraction on 11 April 2023, approximately 9 months prior to the publication of Hulscher et al.[1]

Lastly, the authors provided an estimate that 709 740 people died from COVID-19 vaccination in countries using the Vaccine Adverse Event Reporting System (VAERS). This estimation was obtained by multiplying the 35 487 deaths that were recorded in VAERS as of 16 June 2023 by an assumed underreporting factor of 20, cited from a non peer-reviewed source. However, only a small fraction of the total deaths in VAERS are attributable to the COVID-19 vaccine, which is inconsistent with the claim that 709 740 people have died from the COVID-19 vaccine specifically. The text also fails to acknowledge well-known limitations of using VAERS to generate such estimates, including that VAERS reports are self-reported and are not independently screened by health professionals. Consequently, the use of VAERS data to make this strong causal claim was inappropriate.

In summary, Hulscher et al. attributed 28 deaths to COVID-19 vaccine-induced myocarditis and attempted to extrapolate these findings to discussions on population excess risk associated with COVID-19 vaccination. Research on both the pathophysiological and population-level evidence on vaccine safety is crucial. However, we believe Hulscher et al.'s paper was problematic in two key ways. First, the individual-level causal effects of COVID-19 vaccination on these 28 deaths were poorly justified. Second, the lack of information on myocarditis risk both at baseline and following COVID-19 infection precludes the estimation of excess risk of myocarditis attributable to vaccination in the population. Given these limitations, we believe the conclusions of this review should be restrained to appropriately reflect its study design and methods; the interpretations of findings as causal and discussions of excess population-level risk were inappropriate. Correspondingly, we believe this review fails to appropriately evaluate and communicate the impact of COVID-19 vaccination on myocarditis mortality.

Hannah Van Wyk
Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA

Mia Q. Zhu
Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA

Danielle R. Stone
Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA

Awnish Kumar Singh
Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA

Sarah Bassiouni
Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA
E-mail: sbassiou@umich.edu

Hannah Van Wyk and Mia Q. Zhu have contributed equally to the letter.

References

1. Hulscher N, Hodkinson R, Makis W, McCullough PA. Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis. *ESC Heart Fail* 2024;ehf2.14680. doi:10.1002/ehf2.14680
2. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, *et al*. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med* 2022;**28**:410-422. doi:10.1038/s41591-021-01630-0
3. World Health Organization. Adverse event following immunization: Aide-Mémoire on causality assessment. Accessed March 15, 2024. https://cdn.who.int/media/docs/default-source/pvg/global-vaccine-safety/new-aide-mem-causal-assmt.pdf?sfvrsn=28bed9ea_4
4. Verma AK, Lavine KJ, Lin CY. Myocarditis after Covid-19 mRNA vaccination. *N Engl J Med* 2021;**385**:1332-1334. doi:10.1056/NEJMc2109975
5. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 2015;**12**:14. doi:10.1186/s12982-015-0037-4