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Response to: Van Wyk et al, letter to the editor regarding "Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis"

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We thank Van Wyk et al for their concerns about fatal COVID-19 vaccine induced myocarditis [1]. We agree with Van Wyk et al that papers such as ours should have "major implications for the public's health and perception of COVID-19 vaccination." Van Wyk et al emphasized the importance of covariate information. Because each included case presented a dataset, covariates to the degree that they were disclosed were considered in the adjudication process. We present all available case information in Table 1, including any co-morbities the included studies presented. Adjudicators reviewed all case vignettes described in the original case reports. We found that none of the comorbidities present were the proximate cause of death. In all cases, autopsy findings revealed myocarditis was the primary cause death. Myocarditis has been linked to COVID-19 vaccination for years by the Centers for Disease Control and Prevention (CDC) [2]. When performing autopsies, all possible etiologies are investigated, and the final cause of death is assigned based upon all of the clinical information and judgement of the examiner(s). Van Wyk et al mentioned that the temporality was poorly established in 5 cases that died within two days after vaccination, however, this timeframe is consistent with vaccine production of Spike protein, cardiac inflammation, and resultant lethal arrhythmias. Patone et al found an increased risk of myocarditis in a 28-day window after COVID-19 vaccination [3]. Myocarditis often results in sudden death before any other symptoms appear [4]. Since the time of writing our publication, more evidence has been published supporting the biological mechanisms of fatal COVID-19 vaccine induced myocarditis. Isolated vaccine-induced Spike protein causing cardiovascular inflammation and myocarditis [5,6] may not be the only mechanism(s) of damage. Krauson et al found COVID-19 vaccine mRNA, accompanied by histologically confirmed myocardial injury, in the hearts of individuals that died within 30 days after vaccination [7]. Schreckenberg et al inoculated adult rat cardiomyocytes with mRNA-1273

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(Moderna) and BNT162b2 (Pfizer) and found that they resulted in cellular dysfunctions that are seen in cardiomyopathy [8]. Along with mRNA and the resulting Spike protein, COVID-19 vaccine adjuvants may play a role in COVID-19 vaccine-induced heart damage as described by Kanuri and Sirrkay [9].

We agree with Van Wyk et al's point that the World Health Organization (WHO) criteria should be considered. It should be emphasized that the WHO adverse event following immunization (AEFI) methodology [10] emphasizes the importance of case documents, complete medical history, and autopsy results. For individual assessment, our process met WHO AEFI standards. Van Wyk et al raised the issue of COVID-19 vaccination and myocarditis on a population level. We agree this issue is important but beyond the scope of our manuscript. The U.S. Food and Drug Administration Center for Biologics Evaluation and Research (CBER) has designated a follow-up period of 5 to 15 years for novel genetic products, such as the mRNA COVID-19 vaccines, to observe for any adverse effects that might emerge in the exposed population over time [11]. In 2024, after the present paper was published, the largest COVID-19 vaccine safety study to date, conducted by the Global Vaccine Data Network (GVDN), was published [12]. In this multi-country study, which included approximately 99 million vaccinated individuals, the researchers observed that the risk of myocarditis was notably higher than expected following mRNA COVID-19 vaccinations. Specifically, they found that the risk of myocarditis after dose two from the mRNA-1273 and BNT162b2 vaccines were 6.10 and 2.86 times higher than baseline rates, respectively [12]. Rose et al analyzed the Vaccine Adverse Event Reporting System (VAERS) and found the number of myocarditis reports after COVID-19 vaccination in 2021 was 223 times higher than the average of all vaccines combined for the past 30 years,

concluding that COVID-19 vaccination is strongly associated with a serious adverse safety signal of myocarditis, resulting in hospitalization and death [13].

Van Wyk et al recognized the importance of transparency in the literature search process. In our paper, Figure 1 fully disclosed the numbers of papers screened, reviewed, and included. Since the time of our publication, we are unaware of any missed papers during our review period. We included the papers by Pantazatos [14] and Aarstad [15] in the discussion, because preprints play a vital role in disseminating vital information while papers undergo the months to years long peer-review process [16]. The paper we included by Skidmore [17] was retracted in violation of the Committee on Publication Ethics (COPE) guidelines [18] and republished after peer-review at another journal [19].

The estimate that 709,740 individuals may have died as a result of COVID-19 vaccination, derived by applying an underreporting factor to VAERS data, is indeed an extrapolation that requires careful interpretation and support as Van Wyk et al highlighted. It's been well established that a main limitation of VAERS is underreporting [20, 21], as written in the official VAERS guide to interpreting data [22]. It's estimated that fewer than 1% of vaccine adverse events are reported to VAERS [19]. While there is no official underreporting factor, it's been approximated to fall within the range of 20-40 [13, 14, 23]. Thus, the Pantazatos et al [14] estimated VAERS underreporting factor of 20 that we utilized is a well-supported and conservative estimate. Meissner reported that 86% of VAERS reports were completed by medical professionals or vaccine manufacturers [24]. Healthcare professionals submitting reports to VAERS provide comprehensive clinical vignettes, and their identity and contact information are

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thoroughly documented under penalty of law for false reporting. Thus, it can be inferred that VAERS reports are reliable and fully available for CDC verification.

Overall, since the time of writing our original publication, new findings have provided further support for the population-level associations between COVID-19 vaccination and myocarditis [12, 13]. Additionally, there is now evidence of the deleterious cardiovascular effects induced by COVID-19 vaccine components beyond the Spike protein [5, 6], including mRNA [7, 8] and adjuvants [9]. While Van Wyk and coworkers state, "we believe this review fails to appropriately evaluate and communicate the impact of COVID-19 vaccination on myocarditis mortality", they implicate that indeed this fatal complication may have an even larger public health impact in the future as more reports and completed studies are published. We believe these comments and our conclusions are a strong call for continued vaccine safety vigilance and research aimed at mitigating risk of this fatal outcome after COVID-19 vaccination.

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