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Myocarditis after COVID-19 and influenza infections: insights from a large data set

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In the current issue of *Open Heart*, the study by Butler and colleagues completed a much-needed investigation that provides valuable insights into the risk of developing incident myocarditis in the general population following COVID-19 or influenza infection. The authors used a large, USA-based administrative health claims database to complete a retrospective analysis of the risk of myocarditis following these infections, including a total of 1 219 185 individuals (adults and children) with documented SARS-CoV-2 infection and 634 201 individuals with influenza. The primary result of the study revealed that, while the overall risk of developing myocarditis is low following these viral infections, the risk is profoundly higher after COVID-19 compared with influenza (0.06% vs 0.02%). These translate to rates of 0.73 and 0.24 myocarditis cases per 1000 person-years, respectively. In agreement with prior reports,[1 2] the analysis also found that certain segments of the population are at particularly increased risk for myocarditis post-COVID-19. These include younger males as well as those above 70 years of age. However, the risk distribution for myocarditis was essentially unimodal after influenza, primarily affecting septuagenarians. In addition to age, certain comorbid conditions, including coronary artery disease and prior myocardial infarction, were also established as risk factors in the present analysis.

The authors paid particular attention to maintaining a distinct gap between the study periods; the incidence of influenza-associated myocarditis was assessed between 2016 and 2018, during a period when COVID-19 was not yet known. Although the predominant strain of influenza likely evolved over time, at this time we have no clear evidence to suggest that the risk of adverse events may be different.

Aiming to capture all cases of myocarditis potentially attributable to these viruses, the authors used a 12-month evaluation period based on data from previously published literature.[3 4] The temporal relationship between the index infection and the diagnosis of myocarditis is indeed critically important. In the current report, the median delay in diagnosis among adults was 30 (6, 118) days following COVID-19 and 20 (5, 154) days after influenza. These were different in the paediatric population, where the median delay from infection to myocarditis diagnosis was 27 (8.75, 95) days for COVID-19 and 118 (27, 330) days for influenza. Therefore, the 12-month follow-up duration seems reasonable, yet the clear inverse relationship between diagnostic delay and the certainty of actual causal relationship needs to be emphasised.

Another observation in the current study is the low overall rate of vaccination in the general population both against influenza and SARS-CoV-2 (3.3%). For the latter, the finding may be explained by the study's inclusion period, as newly developed vaccines against COVID-19 first became widely available in late 2020 and early 2021. This may have been a strategic decision made by the authors when designing the study aiming to reduce the effect of potentially confounding elements. While a detailed discussion is beyond the scope of this editorial, it is critical to highlight that, beyond the viral infection itself, an increased incidence of myocarditis has also been reported after receiving COVID-19 messenger RNA vaccination, particularly in young males and the elderly.[5–8] While the exact incidence has been widely debated, it is ultimately believed to represent a rare event, even when compared directly against postviral aetiologies. Based on a retrospective claims-based database analysis, it would essentially be impossible to accurately identify and isolate these cases. Vaccination became virtually universal in 2021, which has likely reduced the risk of

serious complications, including acute post-COVID-19 myocarditis. In a future study, the authors may consider extending their analysis to assess the potential change in rates of postviral myocarditis before and after 2022 as a result of vaccination.

The authors have to be commended for thoroughly considering the potential limitations in their study, many of which are inherent to the design and working with large data sets. Importantly, however, these may gain significance when making clinical decisions at bedside. It is difficult to overlook the highlighted critical gaps physicians face when establishing a diagnosis of myocarditis in routine daily practice, especially considering the potentially associated morbidity and mortality.[4] Key diagnostic tools include endomyocardial biopsy and cardiac MRI.[9] However, aside from select large medical centres, these specialised tests are not broadly available and completing these on an urgent basis may prove logistically challenging even at these sites. Echocardiography, serial biomarker testing and routine electrocardiography may not have the desired diagnostic sensitivity and specificity.

Similarly, fluorodeoxyglucose-positron emission tomography is precise in detecting active inflammation, yet it is a test that is often challenging to complete on an inpatient basis. It requires highly specialised equipment and meticulous patient preparation, and ultimately it is not specific to myocarditis.[10] As the authors acknowledged, a diagnostic test of any kind was only performed in 94.2% of the cohort. Of these, MRI testing was done in 24.7% and endomyocardial biopsy was obtained merely in 1%. While these data represent real-life clinical practice, the lack of confirmatory testing for myocarditis in a large segment of the population not only raises concerns for potential bias but also highlights diagnostic uncertainty. Indeed, this may be offset to some degree by the sheer size of the data set. However, it would be interesting to see a subgroup analysis by the authors that is limited to patients who had at least one, highly specific confirmatory testing performed to establish the diagnosis of myocarditis.

Parallel with the concerns around the diagnostic uncertainty of myocarditis and its causal relationship with influenza/SARS-CoV-2, other potential scenarios also need to be considered that may affect the results of the study. In some cases, infections may remain completely asymptomatic and therefore no diagnostic testing will be pursued, the screening test produces a false negative result or the patient fails to seek medical evaluation despite the presence of viral symptoms. These particular cohorts are even less likely to undergo routine screenings. Therefore, myocarditis may remain completely unnoticed or will only be detected when arrhythmias or other signs/symptoms concerning for heart failure develop. Therefore, vigilance is critically important, especially in populations at heightened risk for complications. Clinicians should have a low threshold to pursue diagnostic testing, potentially cardiac MRI, if available and feasible.

Overall, this large, retrospective claims-based analysis by Butler and colleagues supports a potential link between viral infections (influenza, SARS-CoV-2) and myocarditis in the general population. It also emphasises the need for increased vigilance and early screening of affected patients, particularly those at the highest risk, using diagnostic modalities with the highest specificity.

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