Response by Mills et al Regarding Article, "Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex"

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RESPONSE TO LETTER TO THE EDITOR

Response by Mills et al Regarding Article, "Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex"

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In Response:

We thank Dr Donzelli for their correspondence regarding our recent article in which we evaluated the risk of myocarditis after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and after COVID-19 (coronavirus disease 2019) vaccination in >42 million persons stratified by age and sex.[1]

We extend our previous findings that demonstrate that the risk of myocarditis after SARS-CoV-2 infection is substantially greater than the risk associated with a first dose of ChAdOx1 and a first, second, or booster dose of BNT162b2 mRNA vaccine.[2] However, for all vaccines, the association with myocarditis was stronger in men <40 years of age.[1] In younger men, the risk of myocarditis was higher after a second dose of an mRNA-1273 vaccine than it was after infection.

Dr Donzelli questions whether we have underestimated these risks by restricting our analysis to those admitted to the hospital or dying from myocarditis. This may be the case, but even if systematic testing for myocarditis was performed in all persons with SARS-CoV-2 infection in the community, or in all those who received a COVID-19 vaccine, it is unlikely that our overall conclusion—the risk of myocarditis is substantially greater after infection than vaccination—would change. We agree that active surveillance of adverse reactions after vaccination may provide more precise estimates than passive surveillance. Mansanguan et al applied active surveillance to 301 people 13 to 18 years of age and observed that 1 in 50 had elevated cardiac troponin, and 1 in 100 had possible subclinical myocarditis after a second dose of the BNT162b2 mRNA vaccine.[3] This compared with our observations in which there was just one excess case of clinical myocarditis for every 200 000 young people receiving a second dose of BNT162b2 mRNA vaccine. However, the consequences of asymptomatic transient increases in cardiac troponin levels during infection or after vaccination are highly uncertain. These may be common after many different viral infections or vaccines, and may not be a direct consequence of myocardial inflammation. Indeed, there are many causes of elevated cardiac troponin in this setting,[4] including analytical interference attributable to immunoglobulins binding to fragments of cardiac troponin resulting in macrotroponin complexes.[5]

Dr Donzelli also questioned whether restricting the risk period to 28 days after infection or vaccination may have contributed to an underestimation of risk. This is also possible, as the mechanism through which SARS-CoV-2 infection and COVID-19 vaccination trigger acute myocarditis, and therefore, the precise risk period, are not currently known. However, they are likely to be similar in both scenarios, and by evaluating the same risk period after SARS-CoV-2 infection and COVID-19 vaccination, we can be confident in concluding that the risk is greater after infection. In our time-stratified analysis, the greatest risk was observed in the first 14 days, with comparatively fewer cases presenting subsequently. Additional research to better understand the pathophysiologic basis of myocarditis after viral infection and vaccination will help us to design better surveillance processes and refine and improve our estimates of risk in the future.

ARTICLE INFORMATION

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Disclosures

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Respiratory Virus Threats Advisory Group, and is a member of Scientific Advisory Group for Emergencies COVID-19 group and the National Health Service group, advising on prioritization of monoclonal antibody use for SARS-CoV-2 infection. This research is part of the Data and Connectivity National Core Study, led by Health Data Research United Kingdom (UK) in partnership with the office of National Statistics and funded by UK Research and Innovation (grant ref. MC_PC_20029).

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