

Commentary on: Patone, M., Mei, X.W., Handunnetthi, L. et al. *Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection*. Nat Med (2021). <https://doi.org/10.1038/s41591-021-01630-0> (14 December 2021)

Rick Bradford, 4/1/22

This analysis looks basically sound and establishes statistically significant associations between Covid-19 vaccinations and the occurrence of Myocarditis (with the usual provisos regarding causality). However the reported effect size is very small.

Data is all-England, period 1 Dec 2020 to 24 Aug 2021. The data is not publicly available.

The Paper's Reported Results

The paper estimates the number of extra cases of Myocarditis for two doses of AstraZeneca, Pfizer and Moderna to be 2, 1 and 16 per million people respectively. Compared to baseline they report IRRs (Incident Risk Ratio) as follows...(taken from Tables 3 and 4),

Table: Best estimate of IRR for Myocarditis within 28 days of vaccination when statistically significant (i.e., when 95%CL lower bound IRR exceeds 1), ns = not significant.

IRR	AstraZeneca		Pfizer		Moderna	
	First dose	Second dose	First dose	Second dose	First dose	Second dose
All ages	1.3	ns	1.3	ns	3	10
Under 40	ns	ns	1.8	3.4	4	21
40 or over	1.3	ns	ns	ns	n/a	n/a
Women	1.4	ns	1.5	ns	n/a	n/a
Men	ns	ns	ns	ns	3.8	12

These compare with an IRR within 28 days of a positive test which was reported to be 10 (corresponding to an extra 40 cases per million associated with Covid-19 infection)

Of 397 cases of Myocarditis that were admitted (or died) within 28 days of vaccination, 55 died (14%), of which 29 were men and 26 were women – so the risk of death appears approximately independent of sex. This suggests the extra deaths from Myocarditis following, and associated with, two doses of AstraZeneca, Pfizer and Moderna to be 0.28, 0.14 and 2.2 per million people respectively.

Other Health Conditions

The paper concludes that no extra cases of pericarditis or cardiac arrhythmias are associated with AstraZeneca or Pfizer (though there were with Moderna). I have not investigated this claim. However I note the number of people dying with cardiac arrhythmias within 28 days of vax were far, far larger than deaths from Myocarditis (1,416 women and 1,359 men, Supplementary Table 1) though the mean age was 85.

Critique

IRR or Cases per Million?

We are invited to compare 40 cases per million after Covid infection with smaller case rates per million from vaccination (and by implication that infection is a greater risk than

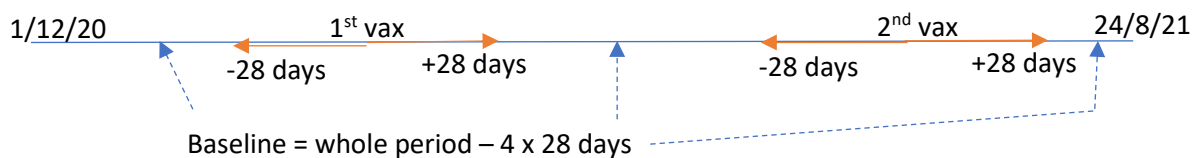
vaccination). However, that is a relative risk comparison, conditional upon becoming infected. I suspect it is better to compare IRR's, in which case Moderna is riskier than infection as regards Myocarditis, especially for the under 40s.

Infection Risk of Myocarditis

The reported incident rate of 40 cases per million after Covid infection is not necessarily attributable to infection alone as the people in question had also been vaccinated. The paper does not address the possibility of synergistic effect between vaccination and infection, analogous to ADE (antibody-dependent enhancement), which is an established phenomenon. This further challenges the implicit claim that infection is more likely to induce Myocarditis than vaccination.

Baseline

My main concern relates to the baseline from which datum a vaccine effect is judged. The paper implicitly assumes that any effect will occur within 28 days. The baseline is then taken as the same calendar period (1st Dec'20 to 24 Aug'21) minus 28 days before and after each vaccination. Diagrammatically...



The 28 days prior to vax is excluded on the basis that an event (e.g., Myocarditis) might cause deferral or cancellation of subsequent vaccination. Sensitivity studies were carried out on the length of this “pre-exposure risk period”. Supplementary Table 8b indicates the sensitivity is not great.

Implicitly the analysis appears self-consistent in that, using this definition of baseline, the 95%CL lower bound IRR only exceeds 1 for 7 days after vax. However, that implicit logic is questionable as the best estimate IRR remains above 1 after 28 days.

I can see nothing in the analysis to support the implicit assumption that the effects of vaccination on Myocarditis might not persist beyond 28 days – perhaps for a year. In which case the baseline is inappropriate and will under-estimate the vaccine effect.

A cleaner analysis might have been obtained using 2019 data for baseline, and using Jan-Nov 2020 for the infection-only effect (prior to vaccine roll-out). The whole of 2021 could then be used with these two baselines to identify vaccine effects without an arbitrary assumption on the duration of any effect.

These changes could only lead to a larger effect assigned to vaccination.

Myocarditis Cases over the Whole Period

Table 4 gives the total number of Myocarditis cases over the 9 month period to be 378 for the under 40s plus 1,231 for ages 40 and over, a total of 1,609. This compares with the pre-Covid data shown below and taken from [Abstract 11463: Epidemiological Trends and Outcomes of Acute](#)

[Myocarditis in the National Health Service of England | Circulation \(ahajournals.org\)](#). In England in 2017 there were 2,000 admissions for Myocarditis, and the graph shows this rate was climbing steeply.

To compare with the 1,609 from this study we would need to account for the study period being 9 months, not 12 months, and also for the fact that the study tracked only vaccinated people, a subset of the whole population. On the other hand, the rate shown by the graph was climbing steeply and might have been 2,500 or 3,000 by 2021. We can only conclude there is not a very obvious gross increase in Myocarditis cases in 2021 attributable to vaccines.

The other interesting observation is the histogram below which shows, contrary to what I thought previously, that Myocarditis is most frequent in young adults, not older adults.

