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University-age vaccine mandates: reply to Lam and Nichols

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We thank Leo Lam and Taylor Nichols for their response[1] to our paper 'COVID-19 vaccine boosters for young adults: a risk–benefit assessment and ethical analysis of mandate policies at universities'.[2] In our paper, we demonstrate that the risk–benefit calculus to mandate boosters for young adults aged 18–29 is a net risk intervention. The authors assert that we have made three inappropriate comparisons of benefits versus risks of the mRNA vaccine booster dose in this age group. We provide our response to each below. We erred on the side of overestimating benefits of the booster dose against severe COVID-19 in this age group and still found net harms to outweigh net benefits. The conclusion of our paper holds, and university booster mandates for young people were—and remain—unethical.

COVID-19 HOSPITALISATIONS PREVENTED VERSUS BOOSTER SERIOUS ADVERSE EVENTS (SAES)

For the first comparison, we weighed predicted hospitalisations prevented by one booster dose of BNT162b2 with vaccine-associated SAEs from the manufacturer's randomised trial (3/5055).[3] We found that the rate of expected SAEs would outweigh the benefits of the booster against hospitalisation by at least 18-fold. Lam and Nichols suggest that this was an inappropriate comparison, as not all SAEs result in hospitalisation. However, the definition of SAE as used in the trial included death, hospitalisation, disability, permanent damage, life-threatening event or condition, which required medical or surgical intervention to prevent a serious outcome.[4] While all comparisons include some degree of incommensurability, comparing these SAEs with hospitalisations prevented by the booster is more reasonable than Lam and Nichols' suggestion of comparing SAEs to infections prevented. The COVID-19 infection hospitalisation risk in this age group was <0.5% (or <1/200)[5] even prior to widespread immunity, thus comparing SAEs to infection risk is entirely inappropriate. Furthermore, a booster dose will only offer transient (if any) protection against infection[6] and cumulative infection rates in the boosted versus unboosted are expected to be approximately the same after several months.[6] We disagree that an SAE from vaccination should be considered equivalent to or in any way comparable with postponing an infection for a few months.

COVID-19 HOSPITALISATIONS PREVENTED VERSUS BOOSTER-ASSOCIATED MYOCARDITIS

For our second comparison, we estimated how many booster-associated myocarditis events would be expected (our estimate was 1.5–4.5 for males) for each COVID-19 hospitalisation prevented. Lam and Nichols contend that 'over 90% of the hospitalised vaccine-caused myocarditis cases fully recovered within days and rarely with long-term health consequences'. In response: first, there have been tragic deaths from vaccine-associated myocarditis.[7–10] Second, at 90 days post diagnosis of vaccine-associated myocarditis, over 25% were still taking medications for the myocarditis diagnosis, over 30% were still on activity restrictions and 54% still had at least one abnormality noted on follow-up cardiac MRI.[11] Third, only 20% of those with postvaccination myocarditis in the same study[11] were listed as having an underlying medical condition. Most of those experiencing vaccine-associated myocarditis would have had a lower-than-average COVID-19 infection hospitalisation rate, highlighting the appropriateness of individualised vaccination and booster policies instead of mandates.

We agree with the authors that it is difficult to directly compare postvaccination myocarditis with COVID-19 hospitalisations prevented when it is unclear what the long-term consequences are in this age group from COVID-19 hospitalisations. But it is important to bear in mind that at least 40% of COVID-19 hospitalisations at the time of our publication were due to an incidental COVID-19 positive test on admission for another diagnosis, and not due to COVID-19.[12 13] These incidental hospitalisations were not removed from our risk–benefit calculation; thus, our analysis likely substantially overestimates booster benefits against hospitalisation in this age group. Furthermore, myocarditis is associated with an increased risk of sudden cardiac death later in life[14] and this should not be trivialised especially when benefits of this booster are questionable and poorly defined owing to increased infection-derived immunity and lack of randomised data of booster effectiveness against severe disease in this age group.

Also, contrary to the statements by Lam and Nichols, we did not use booster myocarditis rates from the Vaccine Adverse Event Reporting System (VAERS), which has consistently underestimated the true rate of postvaccination myocarditis, as noted by Witberg *et al*.[15] Our highest estimated rates of postbooster myocarditis among males in this age group were from the Centers for Disease Control and Prevention (CDC)'s Vaccine Safety Datalink[16] and from the Israeli Military.[17]

Finally, the respondents state: 'The referenced studies,[6 8 9 14] especially those on myocarditis, all concluded that the benefit of vaccination outweighs the risk of a COVID infection, let alone ones that require hospitalisation'.

First, we believe Lam and Nichols mean 'the benefits of vaccination outweigh the risks of *vaccination*'. If that is the case, we note our paper looked at booster doses and only one[16] of the cited studies looked at booster vaccination doses. Second, none of the articles conducted a risk–benefit analysis, with the exception of one[18] comparing postinfectious to postvaccination myocarditis rates, and thus could not and did not attempt to make

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generalisations about overall risks versus benefits. We review with further detail below:

Voleti *et al*[18]: In this systematic review (which did not include booster vaccine doses) the authors conclude '…we found that the risk of incident myocarditis is more than seven times higher in persons who were infected with SARS-CoV-2 than in those who received the COVID-19 vaccines'. However, serious limitations in this analysis include not basing SARS-CoV-2 infection rates on seropositivity, which would overestimate postinfectious risks. They also did not stratify the data by age or sex, which would underestimate postvaccination myocarditis risks to young males. Finally, the authors acknowledge that 'Due to the small number of studies in the infection cohort, we did not assess publication bias for these studies'.

Ahmed *et al*[19]: No risk–benefit analysis was conducted. The authors conclude that 'these findings may help public health policy consider myocarditis in the context of the benefits of COVID-19 vaccination and assess the cardiac condition before the choice of vaccine, which is offered to male adults'.

Witberg *et al*[15]: No risk–benefit analysis was conducted, no comparison to COVID-19 risks was made and this study did not evaluate booster vaccine doses.

Sharff *et al*[16]: No mention of benefit, so no risk–benefit analysis could be performed, but the authors note that 'Myopericarditis occurs after booster doses and may be underreported by current surveillance methods. Completeness or high sensitivity of these case estimates are essential when modeling risk and benefit for wide-scale vaccine implementation and sequential COVID-19 vaccinations for the general population'.

COVID-19 HOSPITALISATIONS PREVENTED VERSUS ≥GRADE 3 REACTOGENICITY

Our third comparison was ≥grade 3 reactogenicity rates versus COVID-19 hospitalisations prevented (1430–4626 to 1). We agree with the authors that these are not directly comparable, but in the setting of the net harms of the booster outweighing the benefits in this age group, as we described in our paper and above, symptoms that prevent normal activities (eg, education) are a relevant source of harm and morbidity, especially since booster doses do not prevent infection long term[6] or transmission[20] to others.

ETHICAL ANALYSIS

Finally, it is worth noting that Drs Lam and Nichols do not engage in any substantial way with our 5-part ethical analysis. They appear to believe that COVID-19 vaccine mandates are a priori ethical and effective. While we will not reiterate in full our arguments, recent policy changes in Europe are consistent with our paper's main conclusions. National health authorities in the UK[21] and across most of Europe are[22 23] or will no longer be[24] even recommending let alone mandating boosters for individuals under 50 without a medical vulnerability. Any small number of European universities which may have initially required vaccination with the primary series have subsequently dropped that requirement. It is worth asking: why are the remaining university booster mandates confined only to a handful of American universities?

CONCLUSION

In conclusion, we have given a fair representation of the expected harms of the booster dose for young people and provided a conservative overestimate of the benefits of the booster dose against severe COVID-19 in this age group. Thus far vaccination has not been shown to prevent future severe disease in those with infection-derived immunity and this is currently estimated to be over 93% of first-year college-aged people in the USA.[25] The benefits of the booster in this age group, even to those not previously infected, have not been demonstrated using randomised data. The CDC's estimate that we used for our benefits calculation was likely to be a confounded estimate of the booster dose's benefits in this age group. For these reasons, and because we did not subtract out incidental hospitalisations, we have constructed this analysis conservatively in assuming the upper limit of possible benefits from the booster dose in this age group.

Even in doing so, we have found net harms to outweigh net benefits in this 18–29-year-old age group. Vaccination, including boosting, does not provide any long-term protection against infection nor decrease transmission risk for more than a few months. As such, the conclusion of our paper holds and university booster mandates for young people were—and remain—unethical.

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