Impact of BMI on COVID-19 vaccine effectiveness

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COVID-19 and obesity are two overlapping pandemics.[1] Individuals with obesity are at risk of developing more severe clinical outcomes as a result of SARS-CoV-2 infection than those without obesity.[2, 3] Obesity is also associated with known risk factors for severe COVID-19, such as diabetes and hypertension. Irrespective of comorbidities, excessive weight results in biomechanical and systemic factors that increase the risk of adverse outcomes. Increased abdominal pressure and upward displacement of the diaphragm result in decreased expiratory reserve volume, functional capacity, and respiratory system compliance. Furthermore, obesity-associated alterations in systemic metabolism include insulin resistance, altered adipokines (eg, increased leptin and decreased adiponectin), and chronic low-grade inflammation.[3] Increased inflammatory chemokines might lead to endothelial dysfunction and exacerbate a prothrombotic state. Preliminary research has shown that mice with obesity have an increased duration of viral shedding due to delayed viral clearance, increased number of secondary bacterial infections, and heightened damage to the respiratory epithelium.[4] In addition, COVID-19 vaccine effectiveness might be lower in people with obesity as baseline alterations in systemic cytokine production might lead to blunted and delayed innate and adaptive immune responses to vaccination.[1] Reduced vaccine effectiveness in people with obesity has been observed for influenza vaccination[5] and preliminary results were suggestive of lower anti-SARS-CoV-2 spike IgG antibody concentrations after two doses of the BNT162b2 mRNA vaccine.[6]

To address the effect of bodyweight on vaccine effectiveness, Carmen Piernas and colleagues[7] in *The Lancet Diabetes & Endocrinology* used a large representative population-based cohort from England of 9 171 524 individuals to investigate severe COVID-19 outcomes after COVID-19 vaccination and associations with BMI. The authors applied multivariable Cox proportional hazard models to estimate the risk of COVID-19 outcomes associated with BMI. Vaccine protection was assessed through a nested matched case-control design to estimate odds ratios in vaccinated versus non-vaccinated people.

Consistent with the findings from phase 3 company-led efficacy trials,[8] the protection of COVID-19 vaccines against severe disease outcomes was high across all BMI categories when comparing people who were vaccinated against those who were unvaccinated. There was a 40–74% lower odds of hospital admission or death after the second dose in all BMI categories, and 90% lower odds after the third dose.

In the vaccinated cohort, people at the two extremes of BMI distribution (very low and very high BMI) were at greater risk of hospitalisation or death from COVID-19 than people of healthy weight. Despite the large sample size, the study was not powered to address variations in vaccine

effectiveness across different vaccine brands and across circulating virus variants. The limitation of their study design was the need to use a matched case-control design, rather than the WHO recommended test-negative design,[9] as the cohort did not include test-negative individuals. Another considerable limitation in interpreting the results for the people who had underweight include potential confounding factors such as frailty, cachexia due to cancer, or other conditions associated with lower BMI, which this study did not capture. Such underlying factors for low weight would inherently have a higher risk of severe COVID-19 outcomes than low weight itself.

There was a high vaccine uptake by people with obesity. Conversely, people who had underweight were less likely to be vaccinated, which might have been an unintended result of public messaging that people with overweight have a higher risk of severe COVID-19, which was corroborated by the UK risk-based strategy of vaccine rollout. These findings should prompt a shift towards more targeted and differentiated public health messaging to enhance vaccine uptake in people who are underweight and who might perceive themselves at lower risk of severe COVID-19.

The finding that vaccine effectiveness is lower in people with higher BMI appears to be robust. Reasons are manifold and might include poorer innate and adaptive immune response.[4] The authors postulate that even with a good serological response there might be an impaired T-cell response that could explain the persistent higher risks of severe COVID-19 outcomes associated with obesity despite vaccination. Vaccine effectiveness increased with a third dose, which underpins the need for a booster to enhance protection.

This large cohort study emphasises the crucial role of obesity in the COVID-19 pandemic. Obesity and COVID-19 appear to be a detrimental intersection, one that has also been observed for influenza and other infectious diseases.[4] Furthermore, people with obesity in the UK have also been affected by the pandemic lockdown measures with increased overeating, reduced physical activity behaviour, and increased barriers to weight management.[10] Tackling obesity as a societal problem now will help mitigate the disastrous consequences of the current COVID-19 pandemic and those of future pandemics.

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