Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL COMMENT

A Tale of 2 mRNA Vaccines

The Spring of Hope, The Winter of Despair*

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The COVID-19 pandemic has transformed messenger RNA (mRNA) vaccines from a working concept to real-world interventions provided to billions worldwide. Few other medical interventions have made such incredible strides in such a short period of time.

Fortunately, these invaluable creations of modern biomedical research have shown excellent effectiveness in preventing infection, symptomatic disease, hospitalizations, severe disease, and mortality associated with COVID-19[1] and were an essential element in the global efforts to curb the pandemic.

However, the unusual circumstances of their development and approval has resulted in lingering concerns regarding their safety in the general public. This concern, in turn, has drawn great attention to reports on vaccine side effects, fueling "vaccine hesitancy," which hampers the ability of vaccination campaigns to achieve their goals of reaching herd immunity. Of these, vaccine-associated myocarditis has, by far, received the most attention. Several studies have shown that mRNA vaccines are associated with an approximately 3-fold increased risk for myocarditis,[2] with the highest risk in young men.[3]

Currently, there is little data comparing the various COVID-19 vaccinations in terms of efficacy and safety. Such data is required as evidence of waning immunity with COVID-19 vaccines[4-7] and the emerging of new viral strains[8-10] both suggest that periodic booster dose vaccinations, whose efficacy has also been shown in large population studies,[11] will continue to be a part of our COVID-19 response for the foreseeable future.[12] To optimize resource utilization, promote a broader compliance with vaccination campaigns, and minimize adverse events, comparisons of the available mRNA vaccines are essential to enable a more tailored approach to COVID-19 vaccination.

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The paper by Naveed at al[13] in this issue of the *Journal of the American College of Cardiology* is an important step toward this personalized and tailored approach to vaccination. Using data from the British Columbia COVID-19 cohort, they compared the incidence of myocarditis, pericarditis, and myopericarditis following primary vaccination with the 2 commercially available mRNA COVID-19 vaccines: the Pfizer BioNTech BNT162b2 and Moderna Spikevax mRNA-1273. Their cohort included >2.2 million individuals vaccinated with BNT162b2 and 870,000 vaccinated with mRNA-1273. The incidence of myocarditis was 12.6 and 33.6 cases per 1 million vaccine doses for BNT162b2 and mRNA-1273, respectively. The adjusted OR for developing vaccine-associated myocarditis with mRNA-1273 compared with BNT162b2 was 2.8 (95% CI: 1.7-4.6). Age- and sex-stratified analysis showed that the increased risk for myocarditis with mRNA-1273 is restricted to men <40 years of age (OR: 3.2; 95% CI: 1.8-5.8 for men; OR: 5.1; 95% CI: 2.7-9.7 for age <40 years).

Use of a cohort-study design for this question serves to both account for adherence to vaccination campaigns and reflect an idealized "optimum" outcome of this population-based intervention.

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This data is important in several respects. First, it provides further data from a high-quality population-based database on the incidence of mRNA vaccine-associated myocarditis. For both vaccines, myocarditis is a very rare adverse event even in the highest-risk population of men <30 years of age (58.1 and 269.7 cases per 1 million vaccine doses for BNT162b2 and mRNA-1273, respectively). This combined with previous data, showing that mRNA vaccine-associated myocarditis is generally a mild disease, associated with low morbidity and mortality, and associated with imaging findings suggesting a benign long-term course,[3] is reassuring in terms of vaccine safety and should help put to rest "vaccine hesitancy" caused by concerns over cardiac adverse events; such a conclusion leans not only on the proven efficacy of the vaccines, but also on data showing that COVID-19 infection is associated with a much higher risk for myocarditis.[2,14]

Second, this is one of only a few direct comparisons of the 2 widely adopted mRNA vaccines, and its results have practical policy implications: for a substantial segment of the population with cardiovascular disease, especially those with left ventricular dysfunction, in whom minimizing risk of myocardial insult is crucial, these data give a strong argument to preferentially use the BNT162b2 vaccine over mRNA-1273. Conversely, in the general population, particularly in those >40 years of age and in the female population as a whole, the results support the equipoise between the 2 vaccines in terms of cardiovascular risks, allowing for health authorities to choose vaccine products according to factors such as cost and availability, which should improve resource utilization. Another patient subgroup whose treatment may be affected by the present results are those who developed vaccine-associated myocarditis and therefore could not complete the full course of primary vaccination or receive booster doses due to concerns of repeat flareups. Under current public health measures, unlikely to change in the near future, such individuals may be severely restricted in terms of employment and travel; strategies to allow such individuals to complete their vaccination course are highly desirable. One option is completing the vaccination course using non-mRNA vaccines. Another option that now comes to mind, considering the results by Naveed et al,[13] is for individuals who developed myocarditis following the mRNA-1273 vaccine to receive the BNT162b2 under close monitoring, perhaps first in the settings of a dedicated study that will examine the safety and efficacy of such a strategy.

The study does have some inherent limitations that merit discussion: inclusion of patients who were diagnosed only during a visit to the emergency department and/or hospitalization may both deflate case numbers as well as represent more severe cases; categorizing patient age as above or below 40 years limits the quality of adjustment and therefore leaves room for substantial residual confounding by age; controlling for comorbidities using an aggregate binary variable further hinders generalizability (immunosuppression cannot be equated with schizophrenia for this matter); and excluding patients with previous myocarditis/pericarditis from the analysis, rather than adjudicating repeat events, limits the ability to discuss real-world risks of mRNA vaccines, as neither diagnosis constitutes a contraindication to immunization presently.

The issue of a tailored approach to COVID-19 vaccination is still in its infancy, and more studies like the one performed by Naveed et al[13] that examine both efficacy as well as additional types of adverse events for primary and booster vaccinations are crucial. In addition, assessments of other strategies to optimize the risk/benefit ratio of vaccination, such as heterologous combinations of vaccine products[15] and schedules,[16] are eagerly awaited.

The COVID-19 pandemic seems to have been curbed in many countries around the world, and everyday life is returning to its prepandemic course. Nevertheless, COVID-19 vaccines are here to stay, and should remain a focus of public health research given their crucial role in preventing repeat outbreaks of the virus.

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