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.

Myopericarditis after COVID-19 vaccination: unexpected but not unprecedented

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In the midst of the devastating COVID-19 pandemic, rapid development of highly effective vaccines was enthusiastically welcomed. Unfortunately, myopericarditis after COVID-19 vaccination was an unanticipated adverse event. In *The Lancet Respiratory Medicine*, Ryan Ruiyang Ling and colleagues commendably review the risk of this adverse event in the context of risk after other vaccines.[1] Their study provides an important perspective on the historical global experience with cardiac adverse events after vaccination.

Ling and colleagues applied rigorous statistical analyses to the available literature and confirmed the conclusions of other reviewers. Specifically, the overall incidence of myopericarditis after COVID-19 vaccination (18·2 cases [95% CI 10·9–30·3] per million doses) is not higher than expected outside of the context of vaccination, and not significantly higher than the incidence of myopericarditis reported after the standard immunisations included in the study, such as influenza vaccines (1·3 [0·0–884·1], p=0·43 *vs* COVID-19 vaccines). There is, however, an important demographic and vaccine-related component to this adverse event that is obscured in reporting the overall incidence. The risk of myopericarditis in young males after their second dose of mRNA COVID-19 vaccine is remarkably higher than expected.

This pattern has been seen before. As Ling and colleagues found when they reviewed the extant literature, myopericarditis risk is well established after receipt of live-replicating smallpox vaccine. Notably, in a study by Oster and colleagues[2] of myocarditis after mRNA COVID-19 vaccination, the rate of myocarditis reported in the highest-risk group of recipients (105·86 cases [95% CI 91·65–122·27] per million doses in males aged 16–17 years receiving a second dose) approached the historical rate of myopericarditis after smallpox vaccination (132·1 cases [81·3–214·6] per million doses) according to Ling and colleagues' study.[1] US military professionals, who are very familiar with adverse events following smallpox vaccination, were among the first to observe myocarditis cases after mRNA COVID-19 vaccines,[3] most likely because the US military includes a large number of young men who received two doses of COVID-19 vaccine very early in the 2021 pandemic vaccine rollout.

Although there are common demographic and clinical features between the myopericarditis cases that followed smallpox vaccine and those that followed mRNA COVID-19 vaccines, better understanding of the pathophysiology of these adverse events following vaccination is an important area for future research. Because smallpox vaccination has very limited global application in the modern era, the experience of mRNA COVID-19 vaccination must now propel the field forward. Analyses of the pathology and immunological mechanisms behind these demographic-dependent adverse events following vaccination are likely to advance our understanding of cardiology and immunology.[4–6] These advances could spur the development of safer vaccines or precision vaccination practices.[7]

Ling and colleagues' analysis[1] also raises important questions about whether cardiac adverse events following vaccination have historically been well evaluated outside of the realm of smallpox vaccine. In a literature review spanning 75 years, it is remarkable that the study team identified only five publications addressing myocarditis following immunisations other than smallpox or COVID-19 vaccination. The 7 million vaccine doses described in these publications represent a small fraction of the billions of vaccinations administered globally every year.[8] This challenge might impact the interpretation of the results. Among the populations who received billions of vaccine doses after which myopericarditis was not observed or very rarely observed, published literature might not exist; reassuring data from background populations would not be captured in analyses of the literature, such as those conducted by Ling and colleagues. The safety signal observed after COVID-19 vaccination is, therefore, even more important to fully investigate.[9]

Reports of unexpected adverse events—albeit rare and limited to a specific subset of vaccine recipients—have the potential to damage vaccine confidence at a crucial point in the pandemic response. Like Ling and colleagues, all professionals who have described myopericarditis following COVID-19 vaccination have emphasised that the benefits of vaccination far outweigh the risks

during the current pandemic. Nonetheless, scientific knowledge and public health strategies must continue to evolve. Alternative vaccine platforms, vaccine doses, or vaccine schedules could reduce the risk of rare adverse events and must be explored in the context of changing infection risk.[10] Vaccine confidence is one our most valuable resources, and it is dependent upon trust in public health. Trust is a fragile commodity that is strengthened by reporting challenges transparently and addressing these challenges with scientific rigour and appropriate concern.

We declare no competing interests.

*Margaret Ryan, Jay Montgomery
m1ryan@ucsd.edu

Immunization Healthcare Division, Defense Health Agency, Falls Church, VA, USA (MR, JM); University of California San Diego, San Diego, CA 92134, USA (MR); Walter Reed National Military Medical Center, Bethesda, MD, USA (JM)

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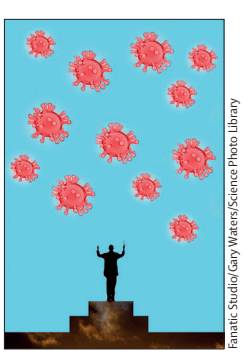
Early-phase clinical trials in a pandemic: learning from the response to COVID-19

The first cases of the novel SARS-CoV-2 virus emerged at the end of 2019 in Wuhan, China. Within 2 months, WHO had declared a public health emergency and the first cases were detected in the UK. The rapid spread of SARS-CoV-2 caused widespread disruption across society and health care, and left little time to plan and design research needed in the context of a new pandemic. Some studies (eg, ISARIC and REMAP-CAP) had pre-existing protocols that were rapidly adjusted, but in most instances, new research studies and clinical trials had to be set up rapidly to respond to the unique environment and challenges created by COVID-19. The success or otherwise of the adaptations made as part of this research response has been highly informative and provides an opportunity to plan effectively for future threats.

The UK adopted a streamlined approach to the delivery of vaccines and therapeutics, capitalising on a single National Health Service (NHS) and the UK National Institute for Health and Care Research (NIHR), a government-funded health research system linked to the NHS. The NIHR Respiratory Translational Research Collaboration (R-TRC) network was in a unique position to coordinate, set up, and conduct early-phase (typically phase 1 and phase 2) clinical trials required to test repurposed or unlicensed drugs for a new disease. Before the pandemic, the R-TRC's main objective was to accelerate delivery of new respiratory drugs via collaborative UK-wide efforts in partnership with industry. In the first few weeks of the pandemic, the R-TRC pivoted to work on mechanistic human immunology studies and phase 2 clinical trials of therapeutics across our ten major teaching hospitals and universities members. We supported one of the first immunology studies on COVID-19 in the UK[1] and used nascent scientific findings to help to select repurposed drugs for early-phase therapeutic trials. Ultimately, the R-TRC helped to deliver 15 phase 2 trials and two large, national phase 2 platform trials,[2,3] and contributed to drug selection via the national centralised UK COVID-19 Therapeutic Advisory Panel process.[4] Here, we discuss our experiences and lessons learned from the first year of the pandemic in the UK[5] and present recommendations for future planning of early-phase clinical trials during a pandemic.



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