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STATE OF THE ART

Anti-SARS-CoV-2 vaccine-induced myocarditis – real but, in general, rare and mild: A consensus statement from the Studies Committee of the Portuguese Society of Cardiology

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Abstract Acute myocarditis (especially) and pericarditis have been consistently associated with the administration of vaccines against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), generating anxiety in the general population, uncertainty in the scientific community and obstacles to ambitious mass vaccination programs, especially in foreign countries.

Like some of its European counterparts, the Portuguese Society of Cardiology (SPC), through its Studies Committee, decided to take a position on some of the most pressing questions related to this issue: (i) How certain are we of this epidemiological association? (ii) What is the probability of its occurrence? (iii) What are the pathophysiological bases of these inflammatory syndromes? (iv) Should their diagnosis, treatment and prognosis follow the same steps as for typical idiopathic or post-viral acute myopericarditis cases? (v) Is the risk of post-vaccine myocarditis great enough to overshadow the occurrence of serious COVID-19 disease in unvaccinated individuals? In addition, the SPC will issue clinical recommendations and offer its outlook on the various paths this emerging disease may take in the future.

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PALAVRAS-CHAVE
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Miocardite induzida pela vacinação anti-SARS-CoV-2 – Real, mas, em geral, rara e ligeira: tomada de posição por parte da comissão de estudos da Sociedade Portuguesa de Cardiologia

Resumo Quadros de miocardite (sobretudo) e de pericardite agudas têm vindo a ser consistentemente relacionados com a administração das vacinas anti-SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus* 2), gerando ansiedade na população geral, incerteza na comunidade científica e entraves aos ambiciosos programas de vacinação maciça, sobretudo em países estrangeiros.

À semelhança de algumas das suas congéneres europeias, pretende a Sociedade Portuguesa de Cardiologia (SPC), por intermédio da sua Comissão de Estudos, tomar posição em relação a algumas da questões mais prementes a si associadas: (i) Quão certos estamos desta associação epidemiológica?; (ii) Qual a probabilidade da sua ocorrência?; (iii) Quais as bases fisiopatológicas destas síndromes inflamatórias?; (iv) Deverão os seus diagnóstico, tratamento e prognóstico seguir os mesmos trâmites dos restantes casos de miopericardite aguda idiopática ou de etiologia pós-vírica?; (v) Será o risco de miocardite pós-vacinal bastante o suficiente a ponto de sobrepujar o da instalação de doença grave por Covid-19 em indivíduos não vacinados? Adicionalmente, serão avançadas recomendações clínicas e perspetivados os diversos trilhos de evolução futura, no respeitante a esta emergente entidade nosológica.

Introduction

The evidence currently pointing to an association between vaccination against COVID-19 (coronavirus disease 2019) and the onset of inflammatory heart disease – principally acute myocarditis, but also acute pericarditis – is, in our view, unequivocal. Many case series from different continents have been published in some of the most important peer-reviewed journals, including the *New England Journal of Medicine* (NEJM),[1–3] the *Journal of the American Medical Association* (JAMA),[4,5] including *JAMA Cardiology*,[6–8] *JAMA Internal Medicine*[9] and *JAMA Network Open*,[10] the *British Medical Journal* (BMJ),[11] *Nature Medicine*,[12] *Circulation*,[13–15] *Vaccine*,[16,17] *Pediatrics*[18] and the *Journal of Pediatrics*.[19,20] Additionally, many others have been pre-published.[21–23] Furthermore, since as early as July last year, the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) had deemed the existence of a causal relationship between anti-SARS-CoV-2 vaccination and the recurring reports of acute myocarditis and pericarditis syndromes as ''probable''.[24–26] For this appraisal, it made use of the Vaccine Adverse Event Reporting System (VAERS) database and, in particular, the Vaccine Safety Datalink (VSD)[27] system. Although it has traditionally been associated with low specificity, generating hypotheses (safety signs) rather than confirming them,[27] the concern is now that this database may be underestimating the actual cases of acute myocarditis induced by anti-COVID-19 vaccines.[21]

In addition to the quantity and diversity of information sources and publications, this link between anti-SARS-CoV-2 vaccines and incident episodes of acute myocarditis is also – or even primarily – reinforced by the notable reproducibility of its presentation pattern: (i) rare and stochastic appearance[1,2,6,12]; (ii) higher risk in adolescents and young adults, especially if male[2,3,25,28]; (iii) tendency to occur after the second vaccine dose, especially with messenger RNA (mRNA) technology – and, among this subgroup, particularly with the mRNA-1273 vaccine (Moderna), rather than the BNT162b2 vaccine (Pfizer-BioNTech)[10–12,22]; (iv) relatively mild clinical manifestations, usually dominated by chest pain and with neither heart failure nor electrical instability[3,15]; and (v) rapid recovery in both clinical and laboratory terms.[3,15]

Moreover, it is not unprecedented for episodes of acute myopericarditis to be causally connected with vaccine-triggered immune responses. In fact, increases in the incidence of such events have been reported in the context of vaccination against hepatitis B, influenza, and historically – and with higher likelihood – smallpox.[29] Interestingly, in these studies, a predisposition for the young male population to be affected was also noted. At all events, this emulates the general epidemiological pattern associated with idiopathic myopericarditis, and not just that of iatrogenic etiology.[26]

Probability of occurrence

Considering the general population, it can be assumed that the risk of post-COVID-19 vaccination acute myocarditis (in particular) and/or pericarditis is very low. For instance, in the NEJM in September 2021, Barda and co-investigators,[1] using data from the largest healthcare provider organization in Israel – including about 1.7 million people (half unvaccinated and half who received the Pfizer-BioNTech BNT162b2 vaccine) – reported 2.7 cases of myocarditis per 100 000 vaccinated individuals. Additionally, in December 2021, also reporting on an Israeli population sample inoculated with

BNT162b2, Mevorach et al.[2] noted the occurrence of only 136 cases of acute myocarditis among more than five million vaccinated individuals. Furthermore, in the same month, Nature Medicine published a paper by Patone and co-workers,[12] who recorded an incidence of acute myocarditis no greater than one case per 100 000 first or second shots of the mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) mRNA vaccines among an English population aged 16 years or older.

However, as stated above, the burden of this inflammatory complication of anti-SARS-CoV-2 vaccination falls asymmetrically on male adolescents and young adults, especially in the setting of the second dose of an mRNA vaccine, and particularly of Moderna's mRNA-1273 vaccine.[2,3,25,28] An analysis of this group's specific risk therefore seems appropriate. Firstly, the importance of young age is well documented. For instance, a third study from Israel, also published in the NEJM,[3] analyzed about 2.5 million individuals aged 16 years or older who were inoculated at least once with the BNT162b2 vaccine. In this case, rather than the general acute myocarditis incidence of 2.1 cases per 100 000 people, a figure of 10.7/100 000 would instead be obtained if only individuals aged between 16 and 29 years were considered. In addition, the previously cited paper by Mevorach et al.[2] lends support to the role of male gender as a major predictor of post-vaccine myocarditis, since, after a second dose of the BNT162b2 vaccine, its likelihood was estimated at about 1/26 000 in men (maximum of 1/6637 among those aged between 16 and 19 years), while reaching only 1/218 000 in women (1/99 853 among those aged between 16 and 19 years). Moreover, the importance of receiving the second rather than the first dose of a COVID-19 mRNA – rather than viral vector – vaccine, in terms of the risk of acute myocarditis, is demonstrated by the study by Patone and co-workers cited above.[12] In this analysis, among a population under the age of 40 and receiving a second shot, its likelihood was estimated at less than 0.5/100 000, about 1/100 000 and 1.5/100 000 after the administration of the viral vector ChAdOx1 (AstraZeneca-Oxford), BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines, respectively. Moreover, in a recent publication in the BMJ[11] encompassing about five million Danes aged 12 years or older, the importance of the commercial formulation of the mRNA vaccine became apparent: the rate of acute myocarditis and/or pericarditis cases diagnosed after immunization with the mRNA-1273 vaccine was 6.3 per 100 000 men and 2 per 100 000 women, whereas the risk attributable to the BNT162b2 vaccine was markedly lower, especially in males: 1.5/100 000 in men and 1.3/100 000 in women.

Pathophysiological bases

Since the epidemiological association between anti-SARS-CoV-2 mRNA vaccines and acute myocarditis and pericarditis has not only been confirmed but also consistently quantified, it seems natural for research to be carried out directed at the pathophysiology underlying the myopericardial inflammation potentially generated by these vaccines. At the present time, its mechanistic basis remains unknown.[26] Nevertheless, several hypotheses have been raised.

The most frequently discussed potential pathophysiological process[26,30,31] is a possible molecular mimicry between the spike protein of SARS-CoV-2 – the biological target of mRNA vaccines – and a particular myocardial structural protein, possibly alpha-myosin. It has been postulated that this may lead to cross-reactivity and thence the synthesis of autoantibodies, which may be harmful to tissue containing the relevant antigens – in this case, the myocardium.[26,30,31] This rationale – similar to that previously conceived for the development of rheumatic heart disease after Lancefield group A streptococcus infection[32] – currently suffers from a lack of laboratory documentation of the theorized cardiac autoantibodies.

Another hypothesis[31] – not incompatible with the first and, by contrast, already backed by basic research, even though carried out in other settings[33–36] – is the possibility of sex hormones exerting differential and even contrasting effects. In this case, the tendency of adolescents and young men to develop post-vaccine myocarditis suggests the possibility of a harmful effect of testosterone, which has previously been repeatedly implicated[33,34] in proinflammatory and poorly adaptive responses, in terms of both injury prevention and repair, at the cardiomyocyte level. By contrast, estrogens have been shown to exert anti-inflammatory effects and to negatively regulate cellular immune responses, mainly in the context of fundamental research undertaken in murine models.[35,36] More broadly, this theory of hormonal modulation of immunoinflammatory processes could explain why male gender represents a prominent risk factor for many other entities in the spectrum of myocarditis[26] – and, most importantly, for the most common idiopathic or viral types, which could include that induced by SARS-CoV-2 itself.[37] On the other hand, the proponents of this hypothesis[33,34] also recognize its main limitation: its inability to explain the apparent cardiac specificity of this biological response.

Finally, and given not only that post-vaccine myocarditis seems to affect a very limited subset of patients (even when all the published studies are grouped and the possibility of reporting underestimation is acknowledged[21]), who, additionally, tend to recover quickly,[3,15] but also that a specific animal model of the condition is currently unavailable, our real ignorance of its pathophysiological basis is likely to persist.[31]

Diagnosis, treatment and prognosis

As mentioned above, the clinical presentation and course of anti-SARS-CoV-2 vaccination-associated myocarditis reveal surprising homogeneity, particularly in its mild intensity and rapid resolution,[3,15] with or without treatment, which is fundamentally supportive.[38] The two largest series published in academic journals to date featuring detailed clinical descriptions are Witberg et al.[3] in the NEJM, with 54 patients, and Truong et al.[15] in *Circulation*, with 139.

With regard to clinical presentation, it is important to highlight that chest pain is by far the most common manifestation, affecting as many as 99% of the patients in the study by Truong et al.,[15] and at least 81% in Witberg et al.[3] The second most common symptom is fever, followed by dyspnea. These were present in 9–31% and 6–27% of these population

samples, respectively.[3,15] It therefore comes as a surprise to us that the CDC-endorsed[24] definition of a confirmed case of post-vaccine myocarditis assigns equal value to all cardiac manifestations – dyspnea, palpitations and syncope as well as chest pain – and does not even include fever.

Concerning complementary assessment, the electrocardiogram (ECG) is, in this setting, most likely to be altered. Between 70% (in the study by Truong and colleagues[15]) and 79% (in Witberg et al.[3]) of these exams show significant abnormalities, particularly of the ST segment (especially elevation, reflecting the concomitant presence of acute pericarditis) and of the T wave, which are present in 68–70% of cases. This naturally bolsters the role of the ECG as a screening tool. In turn, it should be noted that the previously mentioned definition[24] of confirmed post-vaccine myocarditis, as proposed by the CDC, in the absence of histopathological confirmation, requires both elevated troponin and cardiac magnetic resonance imaging (CMRI) findings consistent with myocarditis. The ubiquity of these criteria in the above-mentioned case series[3,15] is therefore to be expected. Even so, elevations of blood biomarkers of myocardial injury are, as a rule, modest[3,15] and global left ventricular systolic function is generally preserved, with mean left ventricular ejection fraction (LVEF) as estimated by CMRI of 60% in the study by Truong and colleagues.[15] In this analysis, the key anomalies detected by this imaging technique were the presence of late gadolinium enhancement, in 76% of patients, and of myocardial edema, in 56%. Importantly, the Lake Louise criteria for myocarditis were met in only 51%. Truong et al.[15] also reported that, on transthoracic echocardiography, only 3% of the sample presented moderate to severe left ventricular systolic dysfunction and only one patient exhibited pericardial effusion, which was small.

Since in this specific context (but also in many others falling within the spectrum of acute myocarditis and chronic inflammatory cardiomyopathy) there have been no randomized controlled clinical trials, nor are there likely to be, assessing patient-centered clinical outcomes,[39] specific treatment cannot be recommended.[26,38] However, as a rule, conventional pharmacotherapy generally initiated in heart failure settings – in particular, angiotensin-converting enzyme inhibitors and beta-blockers – should be considered,[26,38] and escalation to sacubitril-valsartan, mineralocorticoid receptor antagonists and/or sodium-glucose type 2 co-transporter inhibitors may be performed in cases in which moderate-to-severe left ventricular systolic dysfunction is detected.[40] Of course, the clinical indication for all these agents should be reassessed during follow-up consultation.[26,38] There is no contraindication to the use of non-steroidal anti-inflammatory drugs[26,38] if LVEF is not reduced. By contrast, immunomodulatory agents – with the possible exception of colchicine, which is indicated in most cases of associated acute pericarditis[38,41] – should be applied cautiously. In particular, intravenous corticosteroids and immunoglobulins should be considered only in the most severe cases, and always on an individual basis.[38,42] Chest pain can also be addressed with, for example, paracetamol and opioid agents, in addition to the aforementioned non-steroidal anti-inflammatory drugs.[38]

A diagnosis of acute myocarditis mandates hospitalization in the majority of cases, even if its clinical course is expected to be brief and uncomplicated. In this context, Truong et al.[15] report a median of only two days of hospitalization. Therefore, it is not surprising that only two patients in their study[15] and one in that of Witberg and colleagues[3] eventually required pharmacological inotropic or vasopressor support. More importantly, only one patient, reported in the study by Witberg et al.,[3] needed to be rescued with mechanical circulatory support, and none actually died.[3,15] However, it should be noted that other investigators[42] have reported post-COVID-19 vaccine cases of fulminant myocarditis and significant ventricular dysrhythmia. Reassuringly, however, death attributable to these remains an exception.[43]

Comparison with the risk of severe SARS-CoV-2 infection

Although, as described above, the risk of acute myocarditis in the context of anti-SARS-CoV-2 vaccination appears to be real, it seems appropriate to compare it with that of severe COVID-19 disease.[1,24–26] This stems from the fact that the majority of the world's population is likely, sooner or later, to come into contact with SARS-CoV-2.[44,45] Thus, the personal option not to be vaccinated should not, in this context, be interpreted as a risk-free strategy, but rather as the personal selection of a different risk,[45] perhaps an even more serious one.

From early on, the CDC sought to present estimates of the risk-benefit ratio of anti-COVID-19 vaccination.[24–26] While it is indisputable that older age groups – in which the risk of post-vaccine myocarditis is even lower[2,3,25,28] – have significantly more severe infection-related complications,[46,47] the CDC's analysis could have raised doubts in the subgroup that has shown greater predilection toward development of myocarditis, that is, young males,[2,3,25,28] who also happen to be more likely to be spared from severe COVID-19 disease.[46,47] However, such uncertainty may be resolved through a simple case-by-case analysis of the already published data.[24–26] This shows that for every million second doses of anti-SARS-CoV-2 mRNA vaccines administered to this fringe population, 12 000 cases of COVID-19 are expected to be prevented, along with 530 hospitalizations, 127 intensive care unit admissions and three deaths, while only 45–56 cases of acute myocarditis are anticipated to ensue. The study by Barda et al. referred to above[1] also sought to help resolve this dispute, noting that use of the Pfizer-BioNTech BNT162b2 vaccine significantly reduces the risk of numerous other conditions, including acute myocardial infarction, intracranial hemorrhage, pulmonary embolism, deep vein thrombosis, clinically significant dysrhythmia and acute kidney injury, in comparisons between vaccinated and unvaccinated individuals and between infected and uninfected persons. Additionally, other important viral complications, such as systemic inflammatory syndrome in both infants and adults,[48] and post-acute sequelae of the infection in the form of so-called long COVID[49] also appear to be effectively prevented by vaccination.

On the other hand, a favorable risk-benefit balance of anti-SARS-CoV-2 mRNA vaccination can be immediately inferred just by looking at the condition of acute myocarditis per se. Barda et al.[1] have shown that the probability

of this diagnosis increases by a factor of 3.2 after vaccine administration and by 18.3 after COVID-19 infection itself. Additionally, in the study by Patone et al.,[12] with the aforementioned estimate of <1 post-vaccine myocarditis case per 100 000 vaccinated individuals, a 4/100 000 chance of acute myocarditis was ascribed to the unvaccinated population sample. Furthermore, the clinical consequences of post-vaccine and post-infection myocarditis also appear to differ: while the former, as previously stated,[3,15] tends to follow a rapid, mild and uncomplicated course, the latter has been associated – in some[50,51] but not all[52,53] reviews on this matter – with adverse outcomes of various kinds, including death.

Conclusion and future prospects

Based on the currently available scientific evidence, the benefits conferred by anti-SARS-CoV-2 vaccination far outweigh the risks attributed to it,[24–26] particularly with regard to acute myocarditis. Thus, as far as the initially recommended scheme for mRNA vaccine rollout – two doses in all individuals aged 12 years or older[54–57] – is concerned, the Studies Committee of the Portuguese Society of Cardiology recommends its routine use. Although this conflicts with some health policies adopted in northern European countries,[58] it also supports the use of the mRNA-1273 (Moderna) formulation in this setting. In this way, the Committee hopes to contribute decisively to persuading the fringe populations that currently refuse to be vaccinated. Fortunately, regarding the mRNA vaccine rollout in children aged 5–11 years[59] and as a three-dose strategy,[60] no significant warning signs have thus far been detected. In fact, notwithstanding the rather scant scientific evidence currently at our disposal, the risk of acute myocarditis appears to be even lower in these scenarios. Regarding the former, it seems less than that ascribed to young adults, even in males, thus supporting the previously mentioned hypothesis of hormonal modulation of immune phenomena,[31] while as for the latter, the third dose also appears to pose a lesser threat in this instance, at least compared to the second dose. Of course, these observations should not restrict upcoming research in this area. As a matter of fact, the Committee would push for future studies focusing on the evaluation of even lower vaccine doses and longer inter-vaccine intervals in the population with greater predilection toward development of post-vaccine acute myocarditis. On the other hand, by its conditional endorsement of these childhood and booster vaccination strategies, the Committee does not aim to deny the paramount importance of worldwide anti-SARS-CoV-2 vaccination efforts. In fact, it goes as far as to consider that developing countries should even be favored,[61] as it believes this constitutes the most effective means for stemming the emergence of new variants.[62] It is crucial to bear in mind that these – of which Omicron naturally currently has a prominent place[62,63] – may even demonstrate the ability to impact on the favorable risk-benefit ratio currently attributed to vaccination, at least with regard to its effectiveness.

Finally, a challenging situation that some Portuguese cardiologists will have to face over the course of their clinical activity relates to the vaccination of patients with a history – old or recent – of acute myopericarditis. Even though data on this subject are, at present, even scarcer, the Commission recommends, particularly in the context of recent acute myocarditis, that: (a) this population group should not be excluded from vaccination policies; (b) principally in the context of the second vaccine dose, it should be given with one of the two nationally available viral vector formulations – ChAdOx1 (AstraZeneca-Oxford) or Ad26.COV2.S (Johnson & Johnson/Janssen) – even if the first dose had been one using the new mRNA technology.[64–66]

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med. 2021;385:1078–90 [Epub 25.08.21; PMID: 34432976; PMCID: PMC8427535].
2. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N Engl J Med. 2021;385:2140–9 [Epub 06.10.21; PMID: 34614328; PMCID: PMC8531987].
3. Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med. 2021;385:2132–9 [Epub 06.10.21; PMID: 34614329; PMCID: PMC8531986].
4. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 2021;326:1390–9 [PMID: 34477808; PMCID: PMC8511971].
5. Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and pericarditis after vaccination for COVID-19. JAMA. 2021;326:1210–2 [PMID: 34347001; PMCID: PMC8340007].
6. Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol. 2021;6:1202–6 [PMID: 34185045; PMCID: PMC8243257].
7. Kim HW, Jenista ER, Wendell DC, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol. 2021;6:1196–201 [PMID: 34185046; PMCID: PMC8243258].
8. Dionne A, Sperotto F, Chamberlain S, et al. Association of myocarditis with BNT162b2 messenger RNA COVID-19 vaccine in a case series of children. JAMA Cardiol. 2021;6:1446–50 [PMID: 34374740; PMCID: PMC8356143].
9. Simone A, Herald J, Chen A, et al. Acute myocarditis following COVID-19 mRNA vaccination in adults aged 18 years or older. JAMA Intern Med. 2021;181:1668–70 [PMID: 34605853; PMCID: PMC8491129].
10. Beatty AL, Peyser ND, Butcher XE, et al. Analysis of COVID-19 vaccine type and adverse effects following vaccination. JAMA Netw Open. 2021;4:e2140364 [PMID: 34935921; PMCID: PMC8696570].
11. Husby A, Hansen JV, Fosbøl E, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. BMJ. 2021;375:e068665 [PMID: 34916207; PMCID: PMC8683843].
12. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2022;28:410–22 [PMID: 34907393].
13. Rosner CM, Genovese L, Tehrani BN, et al. Myocarditis temporally associated with COVID-19 vaccination. Circulation. 2021;144:502–5 [Epub 16.06.21; PMID: 34133885; PMCID: PMC8340723].

14. Larson KF, Ammirati E, Adler ED, et al. Myocarditis after BNT162b2 and mRNA-1273 vaccination. Circulation. 2021;144:506–8 [Epub 16.06.21; PMID: 34133884; PMCID: PMC8340725].
15. Truong DT, Dionne A, Muniz JC, et al. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults. Circulation. 2022;145:345–56 [PMID: 34865500].
16. Levin D, Shimon G, Fadlon-Derai M, et al. Myocarditis following COVID-19 vaccination – a case series. Vaccine. 2021;39:6195–200 [Epub 04.09.21; PMID: 34535317; PMCID: PMC8416687].
17. Abu Mouch S, Roguin A, Hellou E, et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021;39:3790–3 [Epub 28.05.21; PMID: 34092429; PMCID: PMC8162819].
18. Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in 7 adolescents after Pfizer-BioNTech COVID-19 vaccination. Pediatrics. 2021;148, e2021052478 [Epub 04.06.21; PMID: 34088762].
19. Schauer J, Buddhe S, Colyer J, et al. Myopericarditis after the Pfizer messenger ribonucleic acid coronavirus disease vaccine in adolescents. J Pediatr. 2021;238:317–20 [Epub 03.07.21; PMID: 34228985; PMCID: PMC8253718].
20. Das BB, Kohli U, Ramachandran P, et al. Myopericarditis after messenger RNA coronavirus disease 2019 vaccination in adolescents 12 to 18 years of age. J Pediatr. 2021;238, 26–32.e1 [Epub 30.07.21; PMID: 34339728; PMCID: PMC8321962].
21. Sharff KA, Dancoes DM, Longueil JL, et al. Risk of myopericarditis following COVID-19 mRNA vaccination in a large integrated health system: a comparison of completeness and timeliness of two methods. medRxiv [preprint]. 2021, http://dx.doi.org/10.1101/2021.12.21.21268209.
22. Buchan SA, Seo CY, Johnson C, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. medRxiv [preprint]. 2021, http://dx.doi.org/10.1101/2021.12.02.21267156.
23. Høeg TB, Krug A, Stevenson J, et al. SARS-CoV-2 mRNA vaccination-associated myocarditis in children ages 12–17: a stratified National Database Analysis. medRxiv [preprint]. 2021, http://dx.doi.org/10.1101/2021.08.30.21262866.
24. Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Coronavirus disease 2019 (COVID-19) vaccines; 2021. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html [accessed 06.07.21].
25. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory committee on immunization practices – United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70:977–82 [PMID: 34237049; PMCID: PMC8312754].
26. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation. 2021;144:471–84 [Epub 20.07.21; PMID: 34281357; PMCID: PMC8340726].
27. Shimabukuro TT, Nguyen M, Martin D, et al. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015;33:4398–405 [Epub 22.07.21; PMID: 26209838; PMCID: PMC4632204].
28. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association between COVID-19 and myocarditis using hospital-based administrative data – United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1228–32 [PMID: 34473684; PMCID: PMC8422872].
29. Su JR, McNeil MM, Welsh KJ, et al. Myopericarditis after vaccination, Vaccine Adverse Event Reporting System (VAERS), 1990–2018. Vaccine. 2021;39:839–45 [Epub 06.01.21; PMID: 33422381].
30. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol. 2020;217:108480 [Epub 24.05.20; PMID: 32461193; PMCID: PMC7246018].
31. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nat Rev Cardiol. 2021:1–3 [Epub ahead of print; PMID: 34887571; PMCID: PMC8656440].
32. Tontsch D, Pankuweit S, Maisch B. Autoantibodies in the sera of patients with rheumatic heart disease: characterization of myocardial antigens by two-dimensional immunoblotting and N-terminal sequence analysis. Clin Exp Immunol. 2000;121:270–4 [PMID: 10931141; PMCID: PMC1905712].
33. Heymans S, Eriksson U, Lehtonen J, et al. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. J Am Coll Cardiol. 2016;68:2348–64 [PMID: 27884253].
34. Di Florio DN, Sin J, Coronado MJ, et al. Sex differences in inflammation, redox biology, mitochondria and autoimmunity. Redox Biol. 2020;31:101482 [Epub 04.03.20; PMID: 32197947; PMCID: PMC7212489].
35. Huber SA. Coxsackievirus B3-induced myocarditis: infection of females during the estrus phase of the ovarian cycle leads to activation of T regulatory cells. Virology. 2008;378:292–8 [Epub 30.06.08; PMID: 18586295; PMCID: PMC2596296].
36. Koenig A, Buskiewicz I, Huber SA. Age-associated changes in estrogen receptor ratios correlate with increased female susceptibility to Coxsackievirus B3-induced myocarditis. Front Immunol. 2017;8:1585 [PMID: 29201031; PMCID: PMC5696718].
37. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020;17:1463–71 [Epub 05.05.20; PMID: 32387246; PMCID: PMC7199677].
38. Haaf P, Kuster GM, Mueller C, et al. The very low risk of myocarditis and pericarditis after mRNA COVID-19 vaccination should not discourage vaccination. Swiss Med Wkly. 2021;151:w30087 [PMID: 34668687].
39. Ammirati E, Frigerio M, Adler ED, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. Circ Heart Fail. 2020;13:e007405 [Epub 12.11.20; PMID: 33176455; PMCID: PMC7673642].
40. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726 [Erratum in: Eur Heart J 2021; PMID: 34447992].
41. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36:2921–64 [Epub 29.08.15; PMID: 26320112; PMCID: PMC7539677].
42. Abbate A, Gavin J, Madanchi N, et al. Fulminant myocarditis and systemic hyperinflammation temporally associated with BNT162b2 mRNA COVID-19 vaccination in two patients. Int J Cardiol. 2021;340:119–21 [Epub 18.08.21; PMID: 34416319; PMCID: PMC8372420].
43. Schneider J, Sottmann L, Greinacher A, et al. Postmortem investigation of fatalities following vaccination with COVID-19 vaccines. Int J Legal Med. 2021;135:2335–45 [Epub 30.08.21; PMID: 34591186; PMCID: PMC8482743].
44. Ioannidis JPA. Global perspective of COVID-19 epidemiology for a full-cycle pandemic. Eur J Clin Invest. 2020;50:e13423 [Epub 25.10.20; PMID: 33026101; PMCID: PMC7646031].
45. Gerber JS, Offit PA. COVID-19 vaccines for children. Science. 2021;374:913 [Epub 18.11.21; PMID: 34793207].
46. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020;180:1345–55

[Erratum in: JAMA Intern Med 2021;181:1021; PMID: 32667669; PMCID: PMC7364371].
47. Chen Y, Klein SL, Garibaldi BT, et al. Aging in COVID-19: vulnerability, immunity and intervention. Ageing Res Rev. 2021;65:101205 [Epub 31.10.20; PMID: 33137510; PMCID: PMC7604159].
48. Most ZM, Hendren N, Drazner MH, et al. Striking similarities of multisystem inflammatory syndrome in children and a myocarditis-like syndrome in adults: overlapping manifestations of COVID-19. Circulation. 2021;143:4–6 [Epub 13.08.20; PMID: 32787714].
49. Hageman JR. Long COVID-19 or post-acute sequelae of SARS-CoV-2 infection in children, adolescents, and young adults. Pediatr Ann. 2021;50:e232–3 [Epub 01.06.21; PMID: 34115558].
50. Sawalha K, Abozenah M, Kadado AJ, et al. Systematic review of COVID-19 related myocarditis: insights on management and outcome. Cardiovasc Revasc Med. 2021;23:107–13 [Epub 18.08.20; PMID: 32847728; PMCID: PMC7434380].
51. Ho JS, Sia CH, Chan MY, et al. Coronavirus-induced myocarditis: a meta-summary of cases. Heart Lung. 2020;49:681–5 [Epub 20.08.20; PMID: 32861884; PMCID: PMC7440036].
52. Kariyanna PT, Sutarjono B, Grewal E, et al. A systematic review of COVID-19 and myocarditis. Am J Med Case Rep. 2020;8:299–305 [Epub 05.05.20; PMID: 32747875; PMCID: PMC7397751].
53. Esposito A, Palmisano A, Natale L, et al. Cardiac magnetic resonance characterization of myocarditis-like acute cardiac syndrome in COVID-19. JACC Cardiovasc Imaging. 2020;13:2462–5 [Epub 24.06.20; PMID: 32654966; PMCID: PMC7314439].
54. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603–15 [Epub 10.12.20; PMID: 33301246; PMCID: PMC7745181].
55. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–16 [Epub 30.12.20; PMID: 33378609; PMCID: PMC7787219].
56. Hause AM, Gee J, Baggs J, et al. COVID-19 vaccine safety in adolescents aged 12–17 years – United States, December 14, 2020–July 16, 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1053–8 [PMID: 34351881; PMCID: PMC8367318].
57. Gurdasani D, Bhatt S, Costello A, et al. Vaccinating adolescents against SARS-CoV-2 in England: a risk–benefit analysis. J R Soc Med. 2021;114:513–24 [Epub 01.11.21; PMID: 34723680; PMCID: PMC8649477].
58. Paterlini M. Covid-19: Sweden, Norway, and Finland suspend use of Moderna vaccine in young people ''as a precaution''. BMJ. 2021;375:n2477 [PMID: 34635488].
59. Hause AM, Baggs J, Marquez P, et al. COVID-19 vaccine safety in children aged 5–11 years – United States, November 3–December 19, 2021. MMWR Morb Mortal Wkly Rep. 2021;70:1755–60 [PMID: 34968370].
60. Bar-On YM, Goldberg Y, Mandel M, et al. Protection against Covid-19 by BNT162b2 booster across age groups. N Engl J Med. 2021;385:2421–30 [Epub 08.12.21; PMID: 34879188; PMCID: PMC8728796].
61. Herzog LM, Norheim OF, Emanuel EJ, et al. Covax must go beyond proportional allocation of covid vaccines to ensure fair and equitable access. BMJ. 2021;372:m4853 [PMID: 33402340].
62. Petersen E, Ntoumi F, Hui DS, et al. Emergence of new SARS-CoV-2 variant of concern omicron (B.1.1.529) – highlights Africa's research capabilities, but exposes major knowledge gaps, inequities of vaccine distribution, inadequacies in global COVID-19 response and control efforts. Int J Infect Dis. 2022;114:268–72 [Epub 01.12.21; PMID: 34863925; PMCID: PMC8634699].
63. Kupferschmidt K, Vogel G. Omicron threat remains fuzzy as cases explode. Science. 2022;375:9–10 [Epub 06.01.22; PMID: 34990256].
64. Shaw RH, Stuart A, Greenland M, et al. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Lancet. 2021;397:2043–6 [Epub 12.05.21; erratum in: Lancet 2021; PMID: 33991480; PMCID: PMC8115940].
65. Schmidt T, Klemis V, Schub D, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med. 2021;27:1530–5 [Epub 26.07.21; PMID: 34312554; PMCID: PMC8440177].
66. Stuart ASV, Shaw RH, Liu X, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. Lancet. 2022;399:36–49 [Epub 06.12.21; PMID: 34883053; PMCID: PMC8648333].