Benefits v. risks of COVID-19 vaccination: an examination of vaccination policy impact on the occurrence of myocarditis and pericarditis

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Summary

Studies of myocarditis/pericarditis following mRNA COVID-19 vaccines in Hong Kong have been published. Data are consistent with data from other active surveillance or healthcare databases. The mRNA COVID-19 vaccines have been shown to rarely increase risk of myocarditis, with the highest risk among males aged 12–17 after the second dose. An increased risk of pericarditis has also been shown after the second dose, though less common than myocarditis and more evenly distributed among different sex and age groups. Because of the increased risk of post-vaccine myocarditis, Hong Kong implemented a single dose mRNA COVID-19 vaccine policy on September 15, 2021 for adolescents (age 12–17 years). Post-policy, there were no cases of carditis. 40,167 first dose patients did not receive a second dose. This policy was highly successful in the reduction of carditis, but the trade-off is the potential risk of disease and cost to population-level immunity. This commentary brings forward some important global policy considerations.

Keywords: COVID-19; Myocarditis; Pericarditis; Hong Kong; Males; Adolescents

Several studies of myocarditis/pericarditis following BNT162b2 mRNA COVID-19 vaccination have been reported from Hong Kong. Two vaccines are available in Hong Kong: the BNT 162b2 mRNA COVID-19 vaccine and the Sinovac COVID-19 vaccine. As of December 6, 2022, 3,084,107 (44.7%) of individuals chose the Sinovac COVID-19 vaccine for their primary series and 3,818,096 (55.3%) chose the BNT 162b2 mRNA COVID-19 vaccine. Li et al. conducted a cohort study using the Hong Kong electronic health record database among adolescents who received at least one dose of the BNT 162b2 mRNA COVID-19 vaccine between March 10 and October 18, 2021.[1] Cases were identified through ICD-9 codes. A total of 224,560 first doses and 162,518 s doses were administered to adolescents during the study period. The risk was higher for the second than the first dose and higher among males than females. The estimated number needed to harm (NNH) for the second dose in relation to myocarditis/pericarditis was 2563 for boys and 20,121 for girls aged 12–17 years.

Chua et al. conducted a cohort study of myocarditis/pericarditis in adolescents 12–17 years hospitalized between June 14 and September 4, 2021; cases underwent detailed chart review.[2] The highest risk was after the

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second dose among males, estimating one hospitalized case per 2680 males aged 12–17 years. Lai conducted a case–control study of myocarditis and pericarditis in an inpatient setting from February 23 to August 2, 2021, using ICD-9 codes.[3] Ten controls were matched per case patient based on age, sex, and date of admission. An increased risk was found for BNT162b2 mRNA vaccine with the highest risk among adolescent males. No increased risk of myocarditis and pericarditis was found after receiving the Sinovac COVID-19 vaccine.

These data from Hong Kong are highly consistent with data from other active surveillance or healthcare databases. The mRNA COVID-19 vaccines have been shown to rarely increase risk of myocarditis among males aged 12–17 after the second dose at a rate of about one case per 2500–10,000 vaccinees.[4] As well, the mRNA COVID-19 vaccines have been shown to very rarely cause myocarditis after the first and booster doses, among women, and other age groups at lower levels of risk.[1,2,5–7] The risk of post vaccine myocarditis seems to be higher for the mRNA-1273 vaccine compared to the BNT162b2 mRNA vaccine.[4,8] There are difficulties in direct comparisons and combining data between studies because of variability in the study design, populations being studied, methods for case ascertainment and case definitions, differences in vaccines used and studied, and limitations and differences in how associations are reported. In particular, much of the available data are not adequately stratified by age and gender. An increased risk of pericarditis has also been shown after the second dose of mRNA COVID-19 vaccines, though less common than myocarditis and more evenly distributed among different sex and age groups.[9]

Hong Kong implemented single-dose mRNA COVID-19 vaccine policy

The Joint Scientific Committee of Hong Kong government first lowered the age of recommending BNT 162b2 mRNA COVID-19 vaccination from 16 to 12 years of age on June 10, 2021; the Committee changed the policy on September 15, 2021 to recommended persons aged 12–17 years receive one dose of the BNT162b2 vaccine in light of a sudden surge of post vaccine myocarditis cases in adolescents.[1] The policy of the postponement of the second dose for adolescents applied to both sexes.

At that time, Hong Kong was experiencing only a handful of cases per day, calling into question the risk–benefit equation for adolescents at highest risk of myocarditis particularly among males. Pre-policy (March 10 – September 14, 2021), 224,560 first doses and 162,518 s doses were administered to adolescents: 43 adolescents had a hospitalization for myocarditis following the BNT162b2 mRNA vaccine; 84% (n = 36) of the hospitalizations occurred after the second dose and 5 (12%) were girls.[1] The incidence rate was 3.12 [95% CI: 1.25–6.42] per 100,000 vaccinated patients for the first dose and 22.15 [95% CI: 15.51–30.67] per 100,000 patients for the second dose. The number needed to harm (NNH) for the first dose was 32,051 and for the second dose, 4515.

Post-policy (September 15–October 18, 2021), there were no cases of carditis after 22,245 first doses of the vaccine.[1] Pre-policy, 40,167 first dose patients did not receive a second dose. Based on the second dose NNH, 8.90 (95% CI 6.23–12.32) cases of myocarditis were prevented. Since there was a lack of data on the effectiveness and safety of vaccinating adolescents with the Sinovac COVID-19 vaccine as the second dose after receiving a first dose of the BNT 162b2 mRNA COVID-19 vaccination, the Joint Scientific Committee did not recommend this approach for adolescent vaccination.

Policy analysis

The policy was highly successful in the reduction of carditis, but the trade-off is the potential cost to missed opportunities to benefit from the vaccine and to a lesser extent population-level immunity. The risk-benefit ratio is only favourable in places with a low infection rate such as Hong Kong in 2021 and only as long as cases remain at very low level. Areas where there are outbreaks and prevalent local transmission would not be favourable places for such a policy. The COVID-19 outbreak in Hong Kong (January 2022) which peaked on March 4, 2022 with more than 75,000 cases a day, could be partially related to inadequate protection for adolescents without vaccination or with partial vaccination as a result of this policy. Population immunity is more complex. In theory, reducing the risk of disease among the young male population would improve community immunity. However, waning vaccine immunity limits the potential benefit of vaccinating young males to improve community immunity. Risk benefit calculations on both the individual and societal levels are made by National Regulatory Authorities which at times have come to different conclusions reflecting differences in emphasis of individual vs. societal perspectives, vaccine availability, burden of disease, as well as perhaps other factors. The experience in Hong Kong brings forward the concept of acceptable risk for public health benefit versus individual risk.

These data are quite compelling. Age and sex are the key variables that are robustly associated with the incidence of post vaccine myocarditis. At what point should different vaccines be used for different groups? Should adenovirus vector vaccines or inactivated COVID vaccines be used for those in the risk group for myocarditis or pericarditis? Should the BNT162b2 mRNA vaccine be used preferentially in the high-risk populations of adolescents and young men instead of the mRNA-1273 vaccine? Should population immunity be built, even partially, by people other than young men? It is

important to note that the risk of myocardial injury in healthy young individuals following COVID-19 infection is also high.[10–12] The overall risk-benefit for this gender and age group at highest risk of vaccine-induced myocarditis is heavily dependent on the likelihood of infection without vaccination.

Lengthening the interval between vaccine doses or reducing the individual dosage are other potential options to consider as more data become available. Buchan et al. examined 297 reports of myocarditis and pericarditis following mRNA COVID-19 vaccines in Ontario, Canada.[13] Investigators used Ontario's electronic reporting system for COVID-19 adverse events following immunization. Myocarditis and pericarditis cases following vaccination between the start of the provincial immunization program (December 14, 2020) and September 4, 2021, were recorded. The highest reporting rate of myocarditis and pericarditis was observed in 18–24-year-old males following the mRNA-1273 vaccine as the second doses which was 5.1 (95% CI: 1.9–15.5) time higher than the rate following BNT162b2 mRNA vaccination as the second dose (299.5 v. 59.2 per million doses, respectively). Rates were higher for those who received the mRNA-1273 vaccine for the second dose if they received a heterologous (BNT162b2 mRNA followed by mRNA-1273 vaccination) as opposed to homologous vaccine schedule with an interval of 30 days or less. Ontario subsequently modified its COVID-19 vaccine program on September 29, 2021, for individuals 12–24 years of age to be offered the BNT162b2 mRNA vaccine exclusively. A higher risk for mRNA-1273 than BNT162b2 was found in the United States Vaccine Safety Datalink.[14] However, this differences between mRNA brands was not found in the United States BEST system[15] and often not studied by other myocarditis post-mRNA covid vaccine studies.

The prognosis of myocarditis and pericarditis following mRNA vaccines is generally good, with most persons recovering quickly.[16] Vaccine-induced myocarditis seems to be less severe than myocarditis caused by other factors[17] and medium-term outcomes are also favourable for most persons. However, it is still not clear if these cases will resolve themselves completely or is there a chronic, leftover disease that increases, for example, myocardial infarction risk?[16,17] Does it create a higher risk for cardiac disease effects later in life? Clearly no one can answer such important questions at this point. Therefore, following these post-vaccination myocarditis cases should be one focus of adverse event monitoring globally. Genomic markers of vaccine-induced myocarditis and pericarditis should be a principal research focus once a probable or definite association between the adverse event and vaccination are known. This is an important step in signal validation. The potential underlying mechanism for COVID-19 mRNA vaccine-induced myocarditis has been hypothesized.[18] Innate immune responses leading to inflammation may be triggered by extra RNA species contained in mRNA vaccines, stemming either from manufacturing and/or storage conditions; the RNA molecule is inherently unstable. Heymans and Cooper have also summarized proposed mechanisms of vaccine-induced myocarditis and how these differ from COVID-19-induced cardiac injury.[19] Strongly associated markers between gene variants and adverse event would be helpful in understanding the mechanistic basis of vaccine-induced myocarditis and genomic analysis does not require samples to be collected temporally to the event. Are discovered biomarkers different, for example, from those in patients with inherited forms of myocarditis? If the biomarkers are the same, then the biomarker likely increases the risk for both - those at increased risk of vaccine-induced myocarditis are also likely to be at an increased risk of myocarditis in general. If so, one needs to consider risks and benefits of vaccination in this subpopulation.

Viral infection is the most common cause of myocarditis. Vaccine-induced myocarditis and pericarditis may involve activated immune cells (e.g., eosinophils, cytotoxic T-cells, macrophages), cytokines (e.g., IL-18, IL-27, TNF-alpha), and chemokines (e.g., CXCL9, CXCL10).[20–22] The mechanistic basis of vaccine-induced myocarditis and pericarditis is not yet known but has been reported after smallpox vaccination.[23,24] A case report of two brothers experiencing myocarditis after BNT162b2 mRNA vaccination has been recently published.[24] This report suggests a genetic predisposition to vaccine-induced carditis may exist,[25] something that the Global Vaccine Data Network (GVDN) is pursuing in genomic case control studies.[26]

Global policy considerations

This work brings forward some important global policy considerations. Injury compensation needs to be considered. If this high-risk population needs to be vaccinated for their own protection and to build community immunity, anticipating cases of vaccine adverse events and compensating cases equitably and efficiently is critical. This is particularly true in countries that do not offer government-funded healthcare. A vaccine injury compensation program is available in Hong Kong. Hong Kong citizens who have suffered major complications (including vaccine-induced myocarditis) are eligible to apply for injury compensation. What about low- and middle-income countries where these reactions may not be treated medically?

In wealthy countries, a decision about which vaccines to use to avoid carditis can be made if multiple products are available and we have definitive data on differences in risk by vaccine product. But what about adolescent males and young men in low- and middle-income countries? What do they have the ability to do? If a university or hospital mandates a third or fourth

dose to protect students or patients, do you then need to include safer options? Many of these unanswered questions are why countries should not only consider the use of single vaccine products. Different vaccines likely affect different age groups and sexes. Knowing that SARS- CoV-2 is a global problem, how do we help each other, around the world? Perhaps it comes down to whether we build bridges or walls. These authors hope for more bridges.

Contributors

Bruce C. Carleton - conceptualization, literature search, data analysis and interpretation, writing - original draft.

Dan Salmon - conceptualization, literature search, data analysis and interpretation, writing - original draft.

Ian Wong - conceptualization, writing - review & editing.

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Franciso Lai - epidemiology and outcome of carditis during revision of the manuscript, review and editing.

Declaration of interests

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