PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from Archives of Disease in Childhood but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Myocarditis and myopericarditis cases following COVID-19 mRNA vaccines administered to 12–17-year-olds in Victoria, Australia
AUTHORS	Cheng, Daryl R Clothier, Hazel J Morgan, Hannah Roney, Emma Shenton, Priya Cox, Nicholas Jones, Bryn O Schrader, Silja Crawford, Nigel W Buttery, Jim

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Guido Ehrenfried Pieles Institution and Country: Bristol Royal Hospital, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	09-Feb-2022

GENERAL COMMENTS	The authors describe Australian adolescent data on vaccine associated myocarditis – an extremely important topic, where there is a need for regional accurate and granular data. The introduction and methods are concise, no flaws in study design are detected. Here my specific comments: Introduction: previous studies in children should be discussed more comprehensively, e.g. Jain et all Pediatrics, Oster et al. JAMA, Patone et al Nat Med) , papers on risk vs benefit of vaccination need to be concluded as well to provide an objective introduction of the topic Methods: clear, please provide more detail on reporting pathway (e.g. self reporting vs practitioner hospital, which initial tests BEFORE diagnosis were performed, as these are the factors that can lead to over – or under reporting as mentioned in discussion by authors. Results: more granular clinical data is required! I am aware it is difficult for registry studies to obtain this data, but it is essential to comment on: 1.) arrhythmias? 2.heart function, 3. Specific MRI changes, as indicated in a high proportion, was there oedema? Dysfunction? Fibrosis? As these are the concerning factors. Very important is as well to comment on follow up data, this is the most important question, if myocarditic changes are temporary, and resolved completely, then less concern. Is any follow up available? And if so, what investigations, Discussion: needs to include above papers (and others, just a suggestion) and discuss clinical findings in more detail, and compare in more detail Australian data to other regional data. Discussion on

	follow up needs to be included. Limitations need to be more detailed (bias, over/ underreporting, lack of detailed clinical data etc. Overall this is a very important study and I would recommend publication in a journal such as ADC IF above points are addressed, many of them are essential. Can this be done, then the submitted paper could contribute well to this important topic.

REVIEWER	Reviewer name: Prof. Frances Bu'Lock Institution and Country: East Midlands Congenital Heart Centre, Glenfield Hospital, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	28-Feb-2022

GENERAL COMMENTS	I was pleased to review this interesting short study. I have a number of comments and questions: There is an error in 'what this study adds' What this study adds is wrong.... · 'Incidence of myocarditis post COVID-19 Mrna vaccines are higher after the second dose and appears to differ by age and gender, with younger males being at a higher risk.'... should read 'older males'. You do not describe what presenting symptoms were used for inclusion. You describe that 'ECG abnormalities were observed in 46 (66.7%) cases. An echocardiogram was performed in 66 cases and was abnormal in 8 (12.1%). A cardiac MRI was performed in 30 cases with abnormalities documented in the majority of these (27 cases, 90.0%).' So on what is a diagnosis of myocarditis 2reva made; is it simply 'symptoms' (what symptoms?) or are you basing a diagnosis on an elevalted troponin level only in which case please say so. Also p lease describe the indications for MRIs and what abnormalities were found and how are those whi had MRI different from those who did not. In addition, there I seem to be any control data stated from 2revalen levels in asymptomatic young people post vaccination; was this looked at in clinical trials? Otherwise it is not possible to determine what is the significance of a 2revalen rise in the absence of echo and ECG 2revalence2es. Furthermore, the discussion of gender differences is a little thin; mention of psycholsocial issues, increased 2revalence of other symptom based 'diseases' in females etc. I think these are likely useful data but I a very concerned not to create yet another disease.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments Comments to the Author The authors describe Australian adolescent data on vaccine associated myocarditis - an extremely important topic, where there is a need for regional accurate and granular data. The introduction and methods are concise, no flaws in study design are detected. Here my specific comments: Introduction: previous studies in children should be discussed more comprehensively, e.g. Jain et all Pediatrics, Oster et al. JAMA, Patone et al Nat Med) , papers on risk vs benefit of vaccination need to be concluded as well to provide an objective introduction of

the topic Thank you for reviewing the manuscript. More studies have been included, both in the introduction and in the discussion sections. Studies included focus not only on myocarditis as a whole, but also include papers that specifically address the adolescent population. Methods: clear, please provide more detail on reporting pathway (e.g. self reporting vs practitioner hospital, which initial tests BEFORE diagnosis were performed, as these are the factors that can lead to over - or under reporting as mentioned in discussion by authors. Further details on self vs healthcare practitioner reporting has been included in the method section as suggested. As SAEFVIC is a clinical surveillance database, no tests/investigations are prescribed by SAEFVIC staff; only information is collected on any investigations have been performed. As described in the methods section, all investigations are collected. Assignment of diagnosis (ie. confirm or rejected myocarditis) is then performed by the manuscript authors, regardless of when the tests were done or the diagnosis given by healthcare professionals at time of the case. This is so there is uniform evaluation against a standardised diagnostic criteria. Results: more granular clinical data is required! I am aware it is difficult for registry studies to obtain this data, but it is essential to comment on: 1.) arrhythmias? 2.heart function, 3. specific MRI changes, as indicated in a high proportion, was there oedema? dysfunction? fibrosis? as these are the concerning factors. Further information as requested by reviewers have been included in the results and discussion sections. This includes comments about symptoms including palpitations, as well as investigation findings where available. Unfortunately, it is difficult to draw conclusive evidence on exact clinical presentations, as not all patients had a full suite of investigation findings. Very important is as well to comment on follow up data, this is the most important question, if myocarditic changes are temporary, and resolved completely, then less concern. Is any follow up available? and if so, what investigations, Followup is still ongoing, in line with the ongoing rollout of the COVID-19 vaccination. Data for 1 month followup, including symptoms and exercise restrictions, including breakdown by sex has been included here. Followup MRIs are being performed at 6+ months, so data is not yet available for inclusion in this study. Discussion: needs to include above papers (and others, just a suggestion) and discuss clinical findings in more detail, and compare in more detail Australian data to other regional data. Discussion on follow up needs to be included. Limitations need to be more detailed (bias, over/ underreporting, lack of detailed clinical data etc. Further information regarding clinical findings and Australian data have been included. Data and discussion on followup have been included where available. The limitations section has been modified to include more detail as suggested. This includes specific reference to clinical data etc. Reviewer 2 Comments I was pleased to review this interesting short study. I have a number of comments and questions: THere is an error in 'what this study adds' What this study adds is wrong.... · 'Incidence of myocarditis post COVID-19 mRNA vaccines are higher after the second dose and appears to differ by age and gender, with younger males being at a higher risk.'... should read 'older males'. Thank you for reviewing the manuscript. This has been corrected to be clearer and articulate the risk in adolescent/young adult males You do not describe what presenting symptoms were used for inclusion. You describe that 'ECG abnormalities were observed in 46 (66.7%) cases. An echocardiogram was performed in 66 cases and was abnormal in 8 (12.1%). A cardiac MRI was performed in 30 cases with abnormalities documented in the majority of these (27 cases, 90.0%).' Symptoms as per the Brighton Collaboration criteria have been added into the methods section. So on what is a diagnosis of myocarditis beiing made; is it simply 'symptoms' (what symptoms?) or are you basing a diagnosis on an A confirmed diagnosis of myocarditis was made based on an international collaboration definition for AEFI (Brighton Collaboration). elevalted troponin level only in which case please say so. Also please describe the indications for MRIs and

what abnormalities were found and how are those whi had MRI different from those who did not. This is explained and outlined in paragraph 2 of the methods section. In addition, there doesnt seem to be any control data stated from tropinin levels in asymptomatic young people post vaccination; was this looked at in clinical trials? Otherwise it is not possible to determine what is the significance of a tropinin rise in the absence of echo and ECG abnromalities. Troponin levels were not assessed in clinical trials for vaccines (in either adolescents OR young adults). We have further elaborated and discussed the limitation of just using troponin as the definition for myocarditis. Hence, the usage of international standardised diagnostic criteria which includes but is not limited to troponin. Furthermore, the discussion of gender differences is a little thin; mention of psycholsocial issues, increased prevalance of other symptom based 'diseases' in females etc. The reviewer raises good points around gender impacts. Whilst psychosocial and symptom based conditions may have a female predominance, the diagnosis of myocarditis here is based on objective testing as per Brighton, rather than symptoms alone. Furthermore, the gender difference is clear from epidemiological rates as described in the Methods section, and the troponin differences add to the discussion but are still novel and need further investigation

VERSION 2 – AUTHOR RESPONSE

Editor Comments – 27/04/22 Response You MUST add a manuscript with HIGHLIGHTED changes The updated manuscript has tracked changes to indicate where changes have been made Add information about the Brighton Collaboration criteria for diagnostic certainty. Reference 11 does not give sufficient information. You need to define clearly how you confirmed the diagnosis. We have added Table 1, alongside Reference 11, to fully outline for reviewers and readers what Brighton Collaboration diagnostic criteria entails, and also the levels of certainty. The methods have been strengthened to further expand on how each case was investigated, and the diagnosis confirmed using criteria by two independent reviewers. "There was a clear differential in troponin levels between sexes, with males exhibiting higher and more variable increases in troponin and a median fold rise of 138 times above normal levels" Statements like this need a statistical test and you need to state what is normal level. As the reviewers can appreciate, there are a range of Troponin assays used depending on laboratories, each with their own normal reference range. Hence, it was not feasible for us to list every reference range and normal limit. To facilitate comparison, fold increase above normal was used, as per description in the methods. Discussion "Rigorous clinical review of all cases demonstrated definite or probable diagnoses in all but one case" Please avoid statements like this. Be more cautious and define your exact parameters for diagnosis. Thank you for your comment. The terms definite, probable and possible are Brighton Collaboration labels corresponding to levels of certainty, and are not representative of the authors confidence over diagnosis in a specific case or scenario. Standardised terms from Brighton criteria have been used in line with specific parameters as defined in Table 1 to allow comparison of our data with others. Previous Reviewer 1 Comments Comments to the Author The authors describe Australian adolescent data on vaccine associated myocarditis - an extremely important topic, where there is a need for regional accurate and granular data. The introduction and methods are concise, no flaws in study design are detected. Here my specific comments: Introduction: previous studies in children should be discussed more comprehensively, e.g. Jain et all Pediatrics, Oster et al. JAMA, Patone et al Nat Med) , papers on risk vs benefit of vaccination need to be concluded as well to provide an objective introduction of the

topic Thank you for reviewing the manuscript. More studies have been included, both in the introduction and in the discussion sections. Studies included focus not only on myocarditis as a whole, but also include papers that specifically address the adolescent population. Methods: clear, please provide more detail on reporting pathway (e.g. self reporting vs practitioner hospital, which initial tests BEFORE diagnosis were performed, as these are the factors that can lead to over - or under reporting as mentioned in discussion by authors. Further details on self vs healthcare practitioner reporting has been included in the method section as suggested. As SAEFVIC is a clinical surveillance database, no tests/investigations are prescribed by SAEFVIC staff; only information is collected on any investigations have been performed. As described in the methods section, all investigations are collected. Assignment of diagnosis (ie. confirm or rejected myocarditis) is then performed by the manuscript authors, regardless of when the tests were done or the diagnosis given by healthcare professionals at time of the case. This is so there is uniform evaluation against a standardised diagnostic criteria. Results: more granular clinical data is required! I am aware it is difficult for registry studies to obtain this data, but it is essential to comment on: 1.) arrhythmias? 2.heart function, 3. specific MRI changes, as indicated in a high proportion, was there oedema? dysfunction? fibrosis? as these are the concerning factors. Further information as requested by reviewers have been included in the results and discussion sections. This includes comments about symptoms including palpitations, as well as investigation findings where available. Unfortunately, it is difficult to draw conclusive evidence on exact clinical presentations, as not all patients had a full suite of investigation findings. Very important is as well to comment on follow up data, this is the most important question, if myocarditic changes are temporary, and resolved completely, then less concern. Is any follow up available? and if so, what investigations, Followup is still ongoing, in line with the ongoing rollout of the COVID-19 vaccination. Data for 1 month followup, including symptoms and exercise restrictions, including breakdown by sex has been included here. Followup MRIs are being performed at 6+ months, so data is not yet available for inclusion in this study. Discussion: needs to include above papers (and others, just a suggestion) and discuss clinical findings in more detail, and compare in more detail Australian data to other regional data. Discussion on follow up needs to be included. Limitations need to be more detailed (bias, over/ underreporting, lack of detailed clinical data etc. Further information regarding clinical findings and Australian data have been included. Data and discussion on followup have been included where available. The limitations section has been modified to include more detail as suggested. This includes specific reference to clinical data etc. Previous Reviewer 2 Comments I was pleased to review this interesting short study. I have a number of comments and questions: There is an error in 'what this study adds' What this study adds is wrong.... 'Incidence of myocarditis post COVID-19 mRNA vaccines are higher after the second dose and appears to differ by age and gender, with younger males being at a higher risk.'... should read 'older males'. Thank you for reviewing the manuscript. This has been corrected to be clearer and articulate the risk in adolescent/young adult males You do not describe what presenting symptoms were used for inclusion. You describe that 'ECG abnormalities were observed in 46 (66.7%) cases. An echocardiogram was performed in 66 cases and was abnormal in 8 (12.1%). A cardiac MRI was performed in 30 cases with abnormalities documented in the majority of these (27 cases, 90.0%).' Symptoms as per the Brighton Collaboration criteria have been added into the methods section. So on what is a diagnosis of myocarditis beiing made; is it simply 'symptoms' (what symptoms?) or are you basing a diagnosis on an A confirmed diagnosis of myocarditis was made based on an international collaboration definition for AEFI (Brighton Collaboration). elevalted troponin level only in which case please say so. Also please describe the indications for MRIs and

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VERSION 3 – REVIEW

REVIEWER	Reviewer name: Guido Pieles Institution and Country: United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	11-May-2022

GENERAL COMMENTS	I am reviewing this paper for the second time after having done this for ADC, as the names are published, its also important to say, that I have been majorly involved in the public health response to vaccine associated myocarditis in the UK as expert advisor to UK JCVI, MHRA, CHM and UKHSA and am chair of a working group and guideline on this topic: https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination/myocarditis-and-pericarditis-after-covid-19-vaccination-guidance-for-healthcare-professionals. The authors publish important data that can complement our current knowledge on this topic, in particularly as the incidence in the AUS cohort is slightly higher than observed elsewhere /(1/ million doses). The paper has been approved since I saw the submission last, thank you very much and I will confine the review to addressing points that would still need to be dealt with or explained. Introduction: as suggested previous time, cardiac symptoms and investigations findings in this cohort from other papers need to be written in here in more detail, as it is important to show the reader if we are dealing here with a very mild form of myocarditis or a potentially significant cardiac disease. Methods: as before, simple methodology but without flaw, please review dates of inclusion, does not make sense. Diagnostic criteria: correct Brighton criteria used, these do NOT need to be put in a table in the paper, everyone can read those in the published Brighton criteria. Results: as criticised last time, the clinical and investigational phenotype is very vague, too vague, the authors have attempted to include more details, but are not showing a table of detailed clinical findings (e.g. percentage of chest pain, palpitations, syncope etc - I would suggest to use the Brighton criteria as template and provide

	percentage of the symptoms and findings relevant for this cohort - this is a must for publication, as otherwise the study will be highly criticised for lack of detail and the important information will not be considered truthfully.) iin particuarl: please provide nature of MRI findings (e.g fibrosis, oedema, dysfunction) - while this is a epidemiology paper, cardiologists are in the authorship and I would expect to have more granular (as exactly requested at the last review) data available - if this data is not at hand, then it is questionable how the "definite" Brighton cases have been made. The sex differences have been known, and just the general descriptions of "symptoms" being more pronounced in females, without describing them, is only a minor novel finding, same is true for the Trop, please provide numbers for the trop, as for MRI findings (see above). Table 3 is not entirely clear: how do the symptoms and the exercise restrictions relate to each other/ do they at all, please explain, also say WHAT symptoms remained, this is extremely important to estimate the impact of this condition. Discussion and limitations: should address the main finding of the higher incidence in Australia, and the sex differences. Limitations should address the not very detailed phenoytping. Overall I think this paper has an important message, and should be considered for publication in a journal such as BMJ open, I am slightly confused why the authors did not address the requests by previous reviewers including me, to include more clinical and investigational data, - I do think, this is paramount in improving this paper, and publication in any journal would be hampered by the lack of it, unless it is clearly stated that this data is not available (which of course would question the reliability of the the use of the Brighton criteria here - but it needs to be transparent. If this is addressed I think a publication would be highly recommended. The Victoria health authorities should btw be congratulated on having a vaccination rate in this age group of more than 95%, impressive.

REVIEWER	Reviewer name: Dr. Peter Flom Institution and Country: Peter Flom Consulting, New York, United States Competing interests: None
REVIEW RETURNED	08-May-2022

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. These were fairly straightforward and appropriate and I recommend publication.