British Congenital Cardiac Association Sponsored Audit of SARS-CoV-2 vaccine related myocarditis/myopericarditis in children and young people under 18 years

1. Background

After approval of the Pfizer/BioNTech vaccine for use in children by MHRA, the Joint Committee for Vaccination and Immunisation (JCVI) commenced the process of considering its use in children and young people. In these deliberations, the JCVI were concerned about the possible long-term consequences of a rare vaccine complication of SARS-CoV-2 vaccine related myocarditis/myopericarditis, which has been reported from the USA and Israel, particularly after second vaccine doses and in males.[1,2,3] In a subset of patients including those with mild symptoms, there have been observed acute magnetic resonance imaging (MRI) abnormalities, specifically late gadolinium enhancement (LGE).[1,4] Although rare, these findings (the LGE) raised the possibility of longer-term impacts on cardiac function in cases of SARS-CoV-2 vaccine related myocarditis/myopericarditis, however at this timepoint the evolution of this condition in children and young people is unknown.

A further key consideration is that of risk benefit of SARS-CoV-2 vaccine in children and young people, which has been widely debated. In their initial ruling on July 19th 2021, JCVI noted the low rate of severe illness in healthy children and as such, they initially recommended only a single dose of vaccine in 16-17 year olds and did not recommend vaccination in healthy children aged 12-15 years. Since then, policies regarding SARS-CoV-2 vaccine in children and young people have continued to evolve and become more inclusive, most recently with a recommendation for second doses of Pfizer/BioNTech vaccine for 12-15 year olds on Nov 29th 2021, meanwhile the possibility of vaccination for 5 to 11 year olds remains open. **In this situation, it is crucial that a careful prospective audit of the SARS-CoV-2 vaccine related complication of myocarditis/myopericarditis is undertaken.**

2. Remit and governance

This audit is limited to SARS-CoV-2 vaccine related complication of myocarditis/myopericarditis, which viewed as a clinical priority given the pressing need to understand and document a new disease. Accurate data capture could inform future policies on COVID-19 vaccination as well as the clinical pathway for care of these children and young people.

Data collection (including patient identifiers) by the National Congenital Heart Diseases Audit has specific NHS research ethics and Confidentiality Advisory Group Approval.

Clinical data collected by centres in order to ascertain whether or not the PHE and BCCA protocols for management of SARS-CoV-2 vaccine related complication of myocarditis/myopericarditis was followed can be held as a local audit dataset.

Separate but related activities:
Sharing of de identified data by individual centres with the BCCA team for the purposes of analysis of pooled data will require specific NHS research ethics committee approval.

Data linkage and data analysis related to the epidemiology of SARS-CoV-2 vaccine related complication of myocarditis/myopericarditis using the NHS Digital's Trusted Research Environment (TRE) for England for the CVD-COVID-UK/COVID-IMPACT consortium requires specific approval by a Lay Oversight Panel and the Approval Panel for the Consortium.

3. Scope

Cases meeting the definition for SARS-CoV-2 vaccine related myocarditis/myopericarditis will be included whether they are in the intensive care unit, ward or an outpatient setting not requiring admission, when the case meets the stated criteria. Recent guidance has been published by the UK Health Security Agency[5].

Colleagues within paediatric cardiology networks are encouraged to discuss the patients under the age of 18 years who are suspected of meeting the case definition with the lead paediatric cardiologist responsible for the SARS-CoV-2 Vaccine related Myocarditis/myopericarditis Audit at the relevant paediatric cardiology tertiary centre, see PHE Guideline.
https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination

4. Case definition of Post-vaccine Myocarditis

- Myocarditis and perimyocarditis are defined as a spectrum of disease caused by inflammation of the myocardium (myocarditis) or myocardium and pericardium (perimyocarditis). [6]
- First symptoms commencing within 10 days of Covid mRNA vaccine
- Symptoms and signs may be consistent with myocarditis, pericarditis, or both.
- For surveillance reporting, patients with myocarditis or perimyocarditis should be reported.
- Age range up to 18 years old.
- No other logical explanation for myocarditis presentation.

Please capture all cases of SARS-CoV-2 vaccine related myocarditis/myopericarditis meeting criteria 1) 2) or 3) below.

i) Definitive case (Level 1):

1. Histopathologic examination showing myocardial inflammation. OR
2. Elevated troponin AND EITHER
a. cMRI with myocarditis specific changes.
OR
b. Abnormal echocardiography. Evidence of focal or diffuse depressed left ventricle (LV) function identified by an imaging study, i.e. echocardiography, or that is documented to be of new onset or increased degree of severity. In the absence of a previous study, findings of depressed LV function are considered of new onset if, on follow-up studies, these findings resolve, improve, or worsen.

ii) Probable case (Level 2):

1. Clinical symptoms as for the possible case AND

2. Any 1 of the following 3 findings:
a. Elevated troponin I or T, or CPK MB OR
b. Echocardiogram abnormalities.
OR
c. ECG changes.

iii) Possible case (Level 3)

1. One of the following symptoms: dyspnoea, or palpitations, or chest pain or pressure, or diaphoresis, or sudden death in a patient OR
2. Two of the following symptoms: fatigue, gastrointestinal, dizziness or syncope, oedema, or cough AND
3. Supportive laboratory biomarkers: elevated CRP, or elevated D-dimer, or elevated ESR AND
4. Nonspecific ECG abnormalities: St-T or T waves changes, or premature complexes. AND
5. The absence of evidence of any other likely cause of symptoms or findings.

iv) Not a case

Insufficient evidence (Level 4) to meet level 1, 2, 3 classifications in a reported myocarditis case Not myocarditis (Level 5).
Symptom onset more than 10 days after SARS-CoV-2 vaccine.
Myocarditis caused by SARS-CoV-2 disease.
Myocarditis caused by other identified diseases.

5) Proposed patient assessment and investigations

At all times the clinical condition of the patient should determine the appropriate care setting in terms of the need for hospital admission.
The following parameters form the assessment and drive the case ascertainment:

i) History of clinical symptoms/signs:

1. Chest pain
2. Fever
3. Breathlessness
4. Palpitations

Vaccine type, sequence (1st, 2nd) and date(s)
Interval from vaccine to 1st symptoms:

ii) Blood tests:

To include troponin, FBC, U&Es, LFTs, NT-pro-BNP (or BNP), fibrinogen, D-Dimers, clotting, ferritin, triglyceride, ESR and serum save.

iii) ECG:

ST-elevation (pericarditis), Non-specific ST-T changes, ischaemic changes, arrhythmia.

iv) Echocardiography:

In patients with suspicion for a case of SARS-CoV-2 vaccine related myocarditis/myopericarditis based on i) to iii) undertake echo as soon as practical.
Function (M-mode), valve regurgitation, pericardial effusion, coronary artery changes

v) Cardiac MRI **[Only for level 1-(definitive) and level 2(probable) criteria]**

In cases of SARS-CoV-2 vaccine related myocarditis/myopericarditis undertake cardiac MRI when practicable as soon as possible.
To include assessment of function, pericardial effusion and more specifically for features of myocarditis which include myocardial oedema, hyperaemia or late gadolinium enhancement (Lake Louis Criteria 2009[7] or 2018[8] depending on availability of local normal values for parametric mapping).

v) Follow-up

In the presence of abnormal imaging at initial discharge, consider repeat investigations at 6 months:

- Repeat imaging (Echocardiography +/- Cardiac MRI)
- Repeat ECG
- blood profile panel as at initial presentation.

6) Data collection

i)-iii) are for audit by external bodies. iv) is for local audit of the PHE - BCCA guidelines.

i) For NCHDA

For patients meeting the case definition as stated above, the following data should be submitted to the NCHDA data platform at the relevant tertiary paediatric cardiac centre: the patient identifiers, date of presentation to the tertiary centre (either as inpatient or as outpatient), if admitted the admission and discharge dates, the basic demographics as listed in the NCHDA Data Definitions, the procedure code 130100 - ECHOCARDIOGRAM and the diagnosis code 101167 - VACCINE MYOCARDITIS, as well as any other relevant patient diagnoses (as diagnosis codes 2, 3 etc as applicable) and any other relevant cardiac procedures if applicable (as procedure codes 2, 3 etc as applicable). This data entry is being arranged with NCHDA NICOR and may need to occur from April 2022 (post Qreg5 dataset changes) including both retrospective and prospective cases at that time point.

ii) For MHRA

It is very important that all suspected cases are reported to the Medicines and Healthcare products Regulatory Agency (MHRA) using the COVID-19 Yellow Card scheme. COVID-19 Yellow Card scheme

iii) For Public Health England

https://www.gov.uk/government/publications/covid-19-vaccination-myocarditis-and-pericarditis-information-for-healthcare-professionals/information-for-healthcare-professionals-on-myocarditis-and-pericarditis-following-covid-19-vaccination
A serum sample should be collected from any patient that is suspected of experiencing myocarditis or pericarditis following their first dose of any COVID-19 vaccine and sent to Public Health England (PHE) Colindale. Please use the code 'Heart Inflammation' or 'Myocarditis' for easy identification.

Samples should be sent with a completed E59 sample submission form to:

Dr Kevin Brown
Consultant Medical Virologist
Virus Reference Department
National Infection Service
Public Health England
61 Colindale Avenue
London
NW9 5EQ

iv) For local capture at each centre

In each tertiary paediatric cardiac centre, a local database is to be held by the data manager responsible for the national audit, who will work with the paediatric cardiologist lead for the BCCA Audit to maintain these fields on each child who meets the criteria. The BCCA will supply an excel database and accompanying paper forms for this dataset to each tertiary cardiac centre. The clinical data fields will need to be ascertained by the clinical team and provided to the data managers. The BCCA recommends that the data manager sends a weekly email reminder to the named clinician for an update on any cases.

For each child the NCHDA data manager to hold these items for each child with potential vaccine related complications [e.g. myocarditis/pericarditis][3] To note these are harmonised with the PICANet Custom Audit dataset.

i. Number of doses of vaccine received [choose ONE]: options: 1, 2, 3
ii. Date of most recent vaccine:
iii. Which vaccine [Choose ONE]: options: Pfizer, Moderna

iv. Has the child suffered from COVID-19 infection or PIMS-TS in the past? [Choose ONE] Options: Yes-COVID-19, Yes-PIMS-TS, Yes-both, Neither, Unknown (add date of last vaccine/ COVID infection / PIMS-TS)

v. Symptoms/signs [choose any]
1. Chest pain
2. Fever
3. Breathlessness
4. Palpitation
5. Pericardial effusion
6. Other

vi. Investigations
1. ECG: Options [choose any] ST-elevation (pericarditis), Non-specific ST-T changes, ischaemic changes, arrhythmia
2. Echo: Options [choose any] Impaired myocardial function, Pericardial effusion, Coronary artery changes, valve regurgitation[new]
3. Cardiac enzymes:
a. Peak troponin numerical value
b. Peak NT-pro-BNP
c. Peak BNP

4. Cardiac MR [Choose any]: impaired function, pericardial effusion, myocardial oedema, hyperaemia or late gadolinium enhancement
5. Other

vii. Treatment: options [choose any]: aspirin, steroids, other anti-platelet, inotropes, ACE-I (or) ARB, anti-arrhythmics and/or beta blockers, other, none

viii. Outcome at time point one:
Admission and discharge dates:
If not admitted first assessment by paediatric cardiology date:
Options [choose any]:
complete resolution of signs/symptoms
partial resolution of signs/symptoms
abnormal echo (most recent prior to) at discharge
abnormal MRI (most recent prior to) at discharge
Other-

ix. Outcome at time point two 3-month follow up
1. ECG: Options [choose any] ST-elevation (pericarditis), Non-specific ST-T changes, ischaemic changes, arrhythmia
2. Echo: Options [choose any] Impaired myocardial function, Pericardial effusion, Coronary artery changes, valve regurgitation
3. MR: Complete resolution, Partial resolution

7) References

1. Jain SS, Steele JM, Fonseca B, Huang S, Shah S, Maskatia SA, et al. COVID-19 Vaccination-Associated Myocarditis in Adolescents. Pediatrics. 2021.
2. Dionne A, Sperotto F, Chamberlain S, Baker AL, Powell AJ, Prakash A, et al. Association of Myocarditis With BNT162b2 Messenger RNA COVID-19 Vaccine in a Case Series of Children. JAMA Cardiol. 2021.
3. Mevorach D, Anis E, Cedar N et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. New England Journal of Medicine. 2021
4. Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M. Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: a systematic review and meta-analysis. Circ Cardiovasc Imaging. 2014;7(2):250-8.
5. Myocarditis/pericarditis case definition. 2021; Decatur, GA, USA: Brighton Collaboration of the Task Force for Global Health. Available online: https://brightoncollaboration.us/myocarditis-case-definition-update.
6. https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination
7. Friedrich MG, Sechtem U, Schulz- Menger J, et al; International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic

resonance in myocarditis: a JACC white paper. J Am Coll Cardiol. 2009;53(17): 1475–1487

8. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol. 2018;72(24):3158–3176