**Protocol number: CCU007**

**Title: The impact of COVID-19 and lockdowns on children with congenital heart diseases (CHDs) and their management**

Sub project - CCU007\_01: What are the differences in types of congenital heart disease (CHD) procedures in children during periods of lockdown and relaxation of lockdown, compared to before the COVID-19 pandemic?

**Lay summary**

Children with congenital heart diseases (CHDs) need several operations from when they are born and carrying on into adulthood. During the COVID-19 pandemic surgery for some of these children has been delayed. Delaying surgery could make a child’s condition worse. We do not know what the effect of delayed surgery is on the immediate and long-term health and wellbeing of children with CHDs. We also do not know how vulnerable children with CHDs are to being infected with SARS-CoV-2 (the name of the virus), or once infected to having more serious COVID-19 (illness from being infected), compared with other children. It is possible that they are less likely to be infected because they and their parents shield them from contact with others more so than children without CHDs. On the other hand, if infected, they may be more prone to severe disease, such as that related to heart and lung problems.

We have done a small study in two hospitals that treat children with CHDs. It showed that during the first lockdown operations for less urgent CHDs reduced compared to before COVID. It also showed that the percentage of operations that were urgent increased. Lastly, there were more deaths after surgery during lockdown than before. That study is too small to measure whether the higher death rates were all explained by doing more urgent cases. It also cannot tell us about infection risk or long-term health.

We want to use linked health data from the whole population of England to answer the four questions following this paragraph. For all of these our focus is on children below 16 years of age (<16 ). These questions are registered as four separate projects with the collaboration.

**This document is the protocol for the first of these four questions only** and three separate documents will be written for each of the other three questions. Below we give a very short summary of the analyses we plan to for all four questions, followed by a comprehensive analysis plan for the first question. In each of the protocols we will have a similar introduction and the same set of questions with a brief summary so that readers will know how the question addressed in each specific protocol relates to the broader research planned for children with CHDs. The question that is the focus of each protocol is written with bold font.

1. **What are the differences in types of CHD procedures in children during periods of lockdown and relaxation of lockdown, compared to before the COVID-19 pandemic?**

This will use population comparisons of the types of CHD procedures, how urgent the procedure was and whether it was done as an emergency or in a planned way, as well as the average age of the children, the proportion who had post operative procedures and who died shortly after surgery, between each period of lockdown (first, second, third), the periods of relaxation between these lockdowns, and the period before the pandemic. We will look at whether higher proportions of complications or deaths are due to more operations being done on the most ill children or whether there were additional pandemic related factors. This will be done in data for the whole population of children (defined as ≤ 16 years) with a diagnosis of a CHD in England at the time of the pandemic.

1. **Are there differences in the rates of infection with SARS-CoV-2 between children with CHDs compared to children without CHD? If children with CHDs are infected are they more likely to have severe COVID-19?** We will also explore possible differences between hospital and community acquired infection:
   1. Are there differences in rates of SARS-CoV-2 between children with and without CHDs? Does this differ in relation to hospital or community acquired infection?

This will use data from England, including all children <16 years to compare overall infection rates in children with CHDs to those without CHD. We will also separately compare (a) children with CHD who had surgery/hospital admission during the pandemic to all children in England without CHD; (b) children with CHD who had surgery/hospital admission during the pandemic to children without CHD who had a hospital admission during the pandemic; and (b) children with CHD who did not have surgery/a hospital admission during the pandemic to children in England without CHD.

* 1. In children infected with SARS-CoV-2 are those with CHDs more likely to have severe infection than those who do not have CHD.

These analyses will be restricted to all children in England <16 years who have evidence of SARS-CoV-2 infection. Within that group we will compare fares of admission to ICU, ventilation and death between children with and without CHD.

1. **What are the effects of delays to surgery for CHDs on child’s health and wellbeing over the one to two years following the start of the pandemic?**

This will use individual child data from English general practice and hospital records to compare outcomes between: (a) children with CHD who had surgery delayed and those with CHD who did not have surgery delayed; (b) children with CHD who had surgery delayed and children with other diseases that need surgery who had their surgery delayed and (c) children with CHD who had their surgery delayed with other children in England who did not have known health problems requiting surgery. We will also look at the relationship between length of delay and these outcomes.

1. **What are the long-term consequences of delays in treatment and infection with SARS-CoV2 on the health and wellbeing of children with CHDs?**

We will compare rates of general practice and hospital consultations and new diagnoses or symptoms (e.g. anxiety, sleep problems, fatigue) between: (a) Children with any CHD and children without CHD; (b) Children with CHD who had surgery delay and children with CHD who did not have surgery delay; (c) Children with CHD who had surgery delay and children with other conditions who had surgery delay and (d) children with CHD who had surgery delay and healthy children. We will make similar comparisons between Children who were known to have been infected by SARs-CoV2 and those who do not have evidence of infection, as well as with the same comparison groups as above. We will compare rates of diagnosis of long-covid in children with CHDs who were known to have been infected to the same set of comparison groups. We will explore the possibility of linking health and educational data so that we can compare children with CHD (with and without surgery delay and with and without known infection), to comparison groups as above, in terms of days of school missed, and educational outcomes (e.g. SATs scores, GCSE results). If there is sufficient statistical power, we will look at the proportion of children with CHDs who were vaccinated against COVID and any association of this with health and wellbeing.

**Detailed protocol for Question 1 (CCU007\_01)**

**Background**

Despite rigorous global and UK containment and quarantine efforts, the incidence of infection with SARS-CoV-2 and its morbidity and mortality (i.e. COVID-19) has remained a serious public health problem since it first emerged in early 2020.(1) In the UK the ‘second wave’ starting in early September 2020 resulted in a greater burden on the NHS, more cases and more deaths.(2) Several articles have addressed the reorganisation of surgical activity under COVID-19.(3) However, only a few, if any, have focused on the impact on the management of Congenital Heart Diseases (CHDs) surgery in children.(4–7) Because they are growing children with CHDs have to undergo repeat procedures (surgery or catheterisation) from birth to after their growth spurt is completed. [Note: though subsequent adult surgery may be needed, this project focuses on surgery for CHDs in children below 16 years of age(<16-years)].

We have recently conducted a pilot study from 2 large UK congenital heart surgery institutions, in order to provide initial evidence on outcomes after surgery for CHD during the pandemic and the probability to contract SARS-CoV-2 infection, and the subsequent outcomes, during hospitalisation. Our pilot data showed a marked decline in surgical procedures undertaken in children with CHDs from 166 between 02 Jan 2020 and 22 Mar 2020 (pre-COVID lockdown; mean per day 2.1) to 152 during the first lock down from 23 Mar 2020 to 06 Jul 2020 mean per day 1.4). The case mix also differed between the two time periods. During lockdown surgeries performed were more likely to be urgent and involving younger patients. There was a threefold increase in hospital mortality and increases in acute kidney injury and liver failure, though these were imprecisely estimated with wide confidence intervals that included the null. In this pilot study there were no test positive cases for SARS-CoV-2 infection during hospital stay. These results are based on relatively small numbers and need to be confirmed at national level to reflect case mix and the national distribution of ancestral background, socioeconomic position, etc. This could be done through linkage of the National Congenital Heart Disease Audit, from the National Institute for cardiovascular outcomes research (NICOR), which is a rich source of information including postoperative complications, with national primary and secondary care data, and public health England data.(8,9)

**Research question**

Are there differences in case mix, surgical priority, incidence of mortality and complication after surgery for Congenital Heart Disease (CHD) comparing different periods of lockdown and relaxation of lockdown, to pre-lockdown?

**Objectives**

To compare the following outcomes calculated in groups of children (age < 16 years) with CHDs undergoing surgery/catheterisation between the first lockdown (defined as 23 March 2020 to 23 June 2020), first relaxation (24 June to 04 Nov), second lockdown (05 Nov 2020 to 02 Dec 2020), second relaxation (03 Dec to 05 Jan) and third lockdown (06 Jan 2021 to 07 Mar 2021) each to the reference pre-pandemic period (defined as 01 Jan 2018 to 22 Mar 2020):

1. Types of surgery defined as proportions of the total number of procedures per month in each period

2.  The proportions of procedures that were undertaken at a planned time (elective) and the proportion that were undertaken as an emergency

3. The proportions of procedures with severe complications defined as Unplanned interventions or re-operations, extracorporeal membrane oxygenation (ECMO), necrotising enterocolitis, surgical site infection, prolonged pleural effusion or chylothorax

4. The proportions of deaths within 30 days of a procedure

5. To repeat the main analyses (objectives 1 to 4) in strata (different groups) children’s age, sex, ethnicity, and residential area deprivation in order to understand whether the impact of COVID-19 management on surgical case mix, complications and mortality vary by these characteristics.

**Statistical analysis**

**Population:**  All children (<16-years) in England undergone CHD procedure since 01 Jan 2018 (NCHDA dataset)

Study period: 01 Jan 2018- 31 September 2021(latest date available)

Inclusion criteria

All children (<16-years) in England undergone CHD procedure since 01 Jan 2018 (NCHDA dataset)

Children born after 01 Jan 2002

**Exposure:** Period of national lockdowns and relaxation(10,11)

Pre lockdown :01 Jan 2018 to 22 Mar 2020 (reference)

First lockdown :23 Mar 2020 to 23 Jun 2020

First relaxation : 24 June 2020 to 05 Nov 2020

Second lockdown :05 Nov 2020 to 02 Dec 2020

Second relaxation :03 Dec 2020 to 05 January

Third lockdown :06 Jan 2021 to 07 Mar 2021

Third lockdown relaxation : Step 1 unlock 08 Mar 2021

Step 2 unlock 12 Mar 2021

Step 3 unlock 17 May 2021

Step 4 unlock 21 Jun 2021

**Outcome:**

The specific outcomes for this analysis are

1. Total number of CHD procedures performed per month
2. Proportion of each type of procedures (case mix) per month in each period
3. Proportion of CHD procedures performed on an urgent basis (emergency/non-elective) per month defied by the NCHDA specific procedure list algorithm
4. Proportion of post procedure complications per month defined using the NCHDA complication and mortality lists
5. Proportion of CHD procedures related death (within a period of 28 days from the procedure) per month

Outcome definitions:

*Procedure based episodes:* Episode starts form the date of the first surgical operation to the 30th day. All the subsequent procedures within this 30-day period will be considered as part of the first episode. We will assign the post procedure complication and vital status of the patient at the end of the 30-day period. Any subsequent surgical operation after the 30 days from the start of the first episode will be considered as a new episode.(12)

*CHD case mix*: Defined as the specific procedure grouping as per the PRAiS 2 model. Specific procedure algorithm v 6.03 will be used to derive this from procedure codes from the NCHDA dataset.(13,14)

*Surgical priority:* Categorises the patient in terms of the urgency;

*Elective*: Routine admission from the waiting list.

*Urgent:* Patient’s condition requires urgent intervention (They cannot be sent home without a relevant procedure).

*Emergency*: Unscheduled patients with ongoing cardiovascular compromise or hypoxia. Requirement for procedure within 24 hours irrespective of the time of day.

*Salvage:* Patients in imminent risk of demise without intervention

*Mortality* related to procedure- (*Attribution of death variable from NCHDA dataset*)

*Post operative complications (variable in NCHDA dataset)*

*Unplanned interventions or re-operations-*

*Extra corporeal membrane oxygenation (ECMO) -*

*Necrotising enterocolitis*

*Surgical site infection* -

*Prolonged pleural effusion or chylothorax-*

We will classify the complications into ECMO and non-ECMO for the analysis.

**Covariates**

*Sex*: data from NCHDA (categorical)

*Weight for age ‘z’ score*: data from NCHDA (continuous)

*Height for age ‘z’ score*: data from NCHDA (continuous)

*Age in days*, at date of visit; GP; (Date of visit from NCHDA and Date of birth from GDPPR)

*Severity of illness*: data from NCHDA (categorical)

*Preoperative comorbidity*: Preoperative seizures, comorbidity, pre procedure systemic ventricular ejection fraction, pre-procedure sub pulmonary ventricular ejection fraction, pre-procedure NYHA status, pre-procedure diabetes, history of pulmonary disease, pre-procedure ischemic heart disease, pre-procedural valve or septal defect or vessel size) data from NCHDA (categorical). The complications will be grouped into congenital , acquired, and additional cardiac risk factors(15,16)

*Ethnicity*: (Asian or Asian British, Black or Black British, Mixed, Other ethnic group, and White) data from GDPPR (categorical)

*Deprivation*: Most recent decile of deprivation prior to start of study, defined using 5th of IMD

LSOA scores

**Stratification variable definitions:**

We will explore whether differences in case-mix, including urgency, complications and mortality differ in the following groups.

The group definitions below reflect the ideal but once we have explored the data these may be collapsed if there numbers are too small within some categories for meaningful analyses.

*Age-groups*: early (0-3 months), mid (4-7 months) and late (8-12 months) infancy, early childhood (13-36 months), mid-childhood (37-72 months), late childhood (73-132 months) and adolescence (133-191 months).

*Sex :*

*Ethnicity*: data from HES: (Asian or Asian British, Black or Black British, Mixed, Other ethnic group, and White)

*Deprivation*: Most recent decile (10th) of deprivation prior to start of the study, defined using Index of multiple deprivation (IMD) scores

*Region*: Defined as the highest level of sub-national division of England for administrative purposes: East England, London, Midlands, North West, North East and Yorkshire, South East, and South West (data from GDPPR dataset).

**Analysis:**

The number of CHD procedures per month will be estimated from the NCHDA data. The type of specific procedure grouping (case mix), surgical priority, proportion of death, and any postoperative complications during the different time periods will be compared. We will use Chi-square test to compare the proportion between different time periods and means and standard deviation for the continuous variables will be compared to using appropriate parametric (t-test) or non-parametric (Mann-Whitney’s U) tests. Multivariable logistic regression analysis will be used to estimate the risk of death and postoperative complications related to CHD procedures between pre-pandemic and pandemic time periods after adjusting for the covariates.

Additional analyses will explore whether associations differ by age, sex, geographical region, area deprivation and ethnicity, using categories defined as above but collapsing these if necessary because of small numbers.

**Data sources**

***NHS Digital TRE for England (up to latest release)***

Office of National Statistics (ONS) death registration records

NCHDA- National Congenital Heart Diseases Audit (National Institute for Cardiovascular Outcomes Research (NICOR))

General Practice Extraction Service (GPES) Data for pandemic planning and research GDPPR

**Data Management**

The NCHDA (NICOR) dataset will provide the information related to the CHD procedures like the diagnosis codes, procedure codes, date of the surgery, gender of the child, complications and associated comorbidities. GDPPR dataset will used to link the data for the patient characteristics like date of birth, ethnicity, region, deprivation index etc. The ONS death registration records will be linked to access information on death which were missed in the NCHDA dataset. The individual procedures codes (IPCCCs) will be converted into specific procedure grouping (as used in the PRAiS2 model) by using the ‘specific procedure algorithm v6.03’ from [CCAD - Congenital Analysis - Technical Information (nicor.org.uk)](https://nicor4.nicor.org.uk/CHD/an_paeds.nsf/vwContent/Technical%20Information?Opendocument)(17)

**Patient or user group involvement**

This study does not directly involve patients, however knowledge of impact of COVID-19 on the CHD surgeries is of interest to the public.

**Plans for disseminating and communication study results**

We will publish the results of the study immediately on completion of analyses and paper drafting on a preprint server such as medRxiv (https://www.medrxiv.org/). At the same time as placing on the pre-print server we will submit for open-access peer-reviewed publications. We will disseminate findings to the wider COVID-CVD group, the BHF-NIHR network (including meetings with patients) and through national and international conferences as are appropriate. Depending on the findings, we will also explore additional options for focussed dissemination within appropriate communities. We will make our code available through the BHF Data Science Centre GitHub (<https://github.com/BHFDSC/>) and finalize the protocol prior to commencing analyses.

**Existing resources**

NCHDA approved list of diagnoses and surgical procedures for CHD will be used.(13,18) Also use the specific procedure algorithm v 6.03 for deriving the specific procedure grouping as per NCHDA. 01.specific\_procedure\_algorithm\_v6.05.r and 02.nchda\_aa\_sp\_shared\_codes.r available from [CCAD - Congenital Analysis - Technical Information (nicor.org.uk)](https://nicor4.nicor.org.uk/CHD/an_paeds.nsf/vwContent/Technical%20Information?Opendocument) will be used.

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