

Protocol CCU029 Child hospital admission with COVID-19 – risk factors, risk groups and NHS care utilisation Question 2

2) to explore the changes in characteristics amongst children experiencing a first SARS-CoV-2 infection, over the epidemic waves of SARS-CoV-2 incorporating the Omicron era.

Background

Amongst ~12 million children and adolescents resident in England,¹ between July 2020 and February 2022;² SARS-CoV-2 infection was causal or a contributory factor in the hospitalization of 21,000 individuals.² Since February 2022, children's SARS-CoV-2 exposure histories,³ relevant SARS-CoV-2 testing and health protection policies,⁴ and variant dominance⁵ have evolved. In England, the majority of school age children had detectable SARS-CoV-2 antibodies in March 2022.⁶ This was largely due to infection, especially in younger children, since in October 2023, at least one dose of Covid-19 vaccination had been received in only 9% 5-11 year-olds; 42% 12-15 year-olds and 61% for 16 to 17 year-olds.⁷ Then in English children under 5 years old, Covid-19 vaccination has only been offered to those with significant underlying health conditions.⁸ Increased SARS-CoV-2 immunity may be responsible for the noted drop in incidence of multisystem inflammatory syndrome in children (MIS-C),⁹⁻¹¹ however, the wider impacts of evolving complex inter-related factors upon changes in the phenotypes of pediatric SARS-CoV-2 related hospital admissions are otherwise unclear. Therefore, in this study, we will use population-based electronic healthcare record (EHR) data to describe trends in hospital admissions caused or contributed to by SARS-CoV-2 infection amongst children and adolescent's resident in England. Our study objectives are to explore any changes in the characteristics of hospital admissions caused or contributed to by SARS-CoV-2, including severe admissions involving critical care¹² and in the demographics of affected children, over time.

Methods

Design

National English retrospective cohort study based on linked EHR data.

Data Sources for the linked cohort:

National Health Service (NHS) England's secure data environment (SDE) accessed through the British Heart Foundation Data Science Centre's CVD-COVID-UK/COVID-IMPACT consortium to create a linked cohort comprising the following datasets¹³:

- a) National laboratory Covid-19 testing data from the UK Health Security Agency Second Generation Surveillance System.
- b) Primary care data from the General Practice Extraction Service Data for Pandemic Planning and Research.
- c) Hospital Episode Statistics, including admitted patient care, critical care, and outpatient data.
- d) NHS England's record of Covid-19 vaccination status.

Un-linked national data:

We will describe data from two important national sources of information for contextualisation of the linked cohort:

- a) SARS-CoV-2 prevalence as reported by the UK Office of National Statistics Covid Infection Survey up to its closure in March 2023.⁵
 - b) Deaths for which Covid-19 or MIS-C was listed as a cause on the death certificate as reported by the ONS for each one-year age group between July 2020 and August 2023.¹⁴
- Given the NHS rule that numbers are rounded to multiples of 5 within a linked patient level research dataset, in the context of very small numbers in specific groups, the

unlinked ONS record of individual numbers of deaths provided the most complete picture.

Linked cohort creation

To create our study cohort, datasets will be linked using the NHS number, a unique numeric persistent healthcare identifier assigned at first encounter with the healthcare system. We will analyse the data as presented, leveraging this linkage to ensure the presence of important characteristics (e.g.: date of birth, ethnicity) if one is present across any of the relevant records, but otherwise conducted a complete case analysis, reporting missing variables.

Inclusion Criteria for the cohort

We include children who met all the following criteria: a) age 0 - 17 years old at the time of ascertained SARS-CoV-2 infection, b) residence in England, c) a valid person pseudo-identifier enabling data linkage, d) alive at study start or born during the study period, e) known sex and f) experienced a SARS-CoV-2 related admission to hospital.

Criteria for identifying SARS-CoV-2 related admission:

We use peer reviewed methods to create a cohort of children who had a SARS-CoV-2 related hospitalization in England during the study period of 1 July 2020 to 31 August 2023.

^{15, 16, 2} Hence we consider for inclusion all hospitalisations where at least one of the following criteria is met:

- a) Hospital Episode Statistics recorded the primary or non-primary cause of hospital admission with the ICD-10 codes U07.1 or U07.2, which are the codes for 'Covid 19, with or without a positive test'. OR:
- b) The primary or non-primary cause for admission was an ICD-10 code used to identify MIS-C, known in England as 'Paediatric inflammatory multi-system syndrome (PIMS

TS')¹⁷, which were ICD-10 code U07.5, newly available during 2021; and for 2020 and 2021 only, the ICD-10 codes R65 ('Systemic Inflammatory Response Syndrome'), M30.3 ('Mucocutaneous lymph node syndrome [Kawasaki]'), with no exclude codes that indicate an alternative diagnosis. OR:

c) There was a positive SARS-CoV-2 test from up to 14 days before hospitalisation until the date of hospital discharge.¹⁸

Hospital admission types

Amongst SARS-CoV-2 associated hospitalisations in the cohort, we use a hierarchical approach to identify mutually exclusive hospitalisation types, using a combination of the ICD-10 codes listed as a cause for admission¹⁹ and positive SARS-CoV-2 tests. During this assignment of admission types we firstly identify those with incidental infection (in which SARS-CoV-2 infection is deemed as not causative to the hospital stay^{20, 21}), and then we will remove these records from the study cohort. We report the admission types in Tables 1-2

Table 1

Admission type	Definition
Hospitalisations with nosocomial infection	Where the first evidence of SARS-CoV-2 infection (either based on codes or a positive test) was present from day 8 of hospitalization onwards, consistent with definitions used by NHS England. ¹⁸ Although nosocomial SARS-CoV-2 is not on the causal pathway of the hospital admission, it may contribute to prolonged stay, therefore we considered these to be SARS-CoV-2 related hospitalisations.
Hospitalisations with incidental infection	Candidate reasons for incidental admission, were identified in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) prospective study of covid-19 in children, ²² such as trauma, poisoning, or elective surgery. We included a wider range of primary reasons for admission than ISARIC, capturing also mental health disorders, eye conditions, dental conditions, injuries, assault, self-harm, and certain pregnancy related conditions. ² These children may or may not have had a positive test. After identifying hospital admissions incidental to SARS-CoV-2 infection, we then excluded them from these analyses of SARS-CoV-2 related hospitalisations.
MIS-C hospitalisations	A code for MIS-C was present as a cause for hospitalisation as detailed in 'criteria' and no exclusion codes were present indicating an alternative diagnosis.

Covid-19 hospital admissions	<p>Either the primary cause for admission was a code for Covid-19 (<i>definite Covid-19 admission</i>); OR the primary reason for hospital admission was a sign, symptom, or presentation consistent with Covid-19 (and did not definitively indicate an alternative diagnosis) ²¹⁻²⁵; AND a non-primary cause for hospital admission was covid-19 AND there was no excluded code indicating a reason for hospital admission was an alternative or co-infection (<i>suspected Covid-19 admission</i>). These children may or may not have had a positive test.</p>
Hospitalisations where SARS-CoV-2 infection was a contributor	<p>A non-primary reason for admission was Covid-19 AND the primary cause for admission was a condition known to co-occur with SARS-CoV-2 infection as a co or secondary infection, such as respiratory syncytial virus, parainfluenza, adenovirus, staphylococcal pneumonia, streptococcal pneumonia) ^{26, 27 28}; OR was a condition that has been linked to SARS-CoV-2 infection in children ^{27, 28} (type 1 diabetes mellitus, status epilepticus or febrile seizures); OR was a condition associated with higher risk of severe illness with SARS-CoV-2 infection ^{21, 22}(conditions treated with immunosuppression, any cancer, neurodevelopmental conditions that may affect breathing, neonatal conditions such as poor feeding, respiratory diseases such as asthma). These children may or may not have had a positive test.</p>

Table 2: Information on admission type codes for stated groups of SARS-CoV-2 associated hospital admissions

Type of Admission	<p style="text-align: right;">Criteria for Inclusion</p> <p>ICD-10 Codes presented in the format provided by the World Health Organisation 2019: https://icd.who.int/browse10/2019/en</p> <p>Where we present a code as a single letter, then we include the whole chapter (eg: C); where we present a code as a letter with a single number (eg: C0) we include all codes starting with this letter number combination; where we present a code as a letter with two numbers (eg: C00) we include all codes starting with this letter number combination; and where we present a code with a letter and three numbers with a decimal point (eg: C00.0) we include only this specific code.</p>
Hospitalisation associated with Nosocomial SARS-CoV-2 infection	A first associated Positive SARS-CoV-2 test between day 8 of hospitalisation and hospital discharge and / or first presence of Covid codes U07.1, U07.2 (and U07.3, U07.4 only in primary position) amongst causes for hospitalisation from episodes starting after day 8 of the admission.
Type C (Incidental) (Hospitalisation associated with incidental SARS-CoV-2 infection)	<p>Mental health, eye conditions, dental conditions, injuries, trauma, assault, self-harm, poisoning, surgical problems such as those affecting hernia, bowel or testis, certain pregnancy related conditions, neonatal disorders with clear non covid related aetiology, infections with no known link to SARS-COV-2, skin disorders, health care process codes excepting isolation cubicles.</p> <p>The above are represented by the following codes / chapters in a primary diagnostic position:</p> <p>A00, A01, A02, A03, A04, A05, A06, A07, A08.0, A08.1, A08.2, A15, A16, A17, A18, A19, A2, A3, A5, A6, B00, B01, B02, B03, B04, B05, B06, B07, B08, B1, B2.6, B3, B4, B5, B6, B7, B8, D1, D2, D30, D31, D32, D33, D34, D35, D36, D50, D51, D52, D53, D63.8, D64.9, D68.9, D69, D73, E0, E15, E16, E2, E3, E5, E87, F0, F1, F2, F3, F4, F5, F6, F70, F71, F80, F81, F82, F9, G0, G25.0, G25.1, G25.2, G25.3, G25.4, G25.5, G25.6, G25.8, G43, G44, G5, G6, G9, H, I01, I02, I33, I38, I39, I6, I7, I8, J6, J95, K0, K1, K2, K3, K4, K55, K56, K58, K59, K6, K77, K8, K91, K92, K93, L0, L2, L3, L4, L5, L6, L72, L73, L8, L9, M00, M01, M02, M03, M1, M2, M4, M5, M6, M7, M8, M9, N10, N14, N16, N2, N3, N39, N4, N5, N6, N7, N8, N9, O, P00, P01, P02, P03, P04, P08, P1, P20, P21, P24, P26, P3, P50, P51, P52, P53, P54, P55, P56, P57, P58, P59, P6, P70, P71, P72, P75, P76, P77, P78, P8, P90, P91, P94, P95, P96, Q1, Q38, Q5, Q66, Q68, Q69, Q70, Q71, Q72, Q73, Q74, Q82, Q84, Q86, Q95, Q96, Q97, Q98, Q99, R04, R01, R03, R09, R12, R14, R15, R19, R20, R22, R23, R25, R26, R27, R29.0, R29.1, R29.2, R29.4, R30, R31, R32, R33, R35, R39, R44, R45, R46, R47, R60, R61, R63.1, R63.2, R68.0, R76.8, R80, R81, R82, R89, R90.0, R93, U07.0, U07.6, U82, U83, S, T, V, W, X, Y, Z</p> <p>Excluding these codes representing different subgroups in primary positions, and the three PIMS-TS related codes (U07.5, M30.3, R65) in non-primary positions:</p> <p>B30.9, B33.8, B34, H66.9, I88.0, K29.7, K44, K85.9, Y4, Y5, Z03.8, Z03.9, U07.5, M30.3, R65</p>
<p>Multisystem inflammatory syndrome in children (MIS-C)</p> <p>Paediatric Inflammatory Multisystem Syndrome with a temporal association with SARS-COV-2 (PIMS-TS)</p>	<p>PIMS-TS code in any diagnostic position (U07.5, M30.3, R65), and in the case of M30.3 and R65, none of the following exclude codes that indicate a diagnosis of sepsis or bacterial diseases may be more likely than PIMS-TS:</p> <p>A00, A01, A02, A03, A04, A05, A06, A07, A08.0, A08.1, A08.2, A17, A18, A19, A2, A3, A4, A5, A6, A7, A80, A81.0, A81.1, A81.2, A82, A83, A84, A85, A87.0, A87.1, A88.0, A88.1, A9, B01, B02, B03, B04, B05, B06, B07, B08, B15, B16, B17, B18, B2, B30.0, B30.1, B30.3, B33.0, B33.1, B33.3, B33.4, B34.0, B34.1, B34.3, B34.4, B4, B5, B6, B7, B8, B90, B91, B92, B94, B95, B96, B97.0, B97.1, B97.3, B97.4, B97.5, B97.6, B97.7, B98, C, D37, D38, D4, D5, D60, D61, D62, D63, D65, D66, D67, D8, E88.3, G00, G01, G02, G03.0, G03.1, G03.2, G04.1, G04.2, G05, G06, G07, G08, I0, I31, I32, I35, I36, I37, I38, I39, Q2, J02.0, J03.0, J09, J10, J11, J12.0, J12.1, J12.2, J12.3, J13, J14, J15, J16.0, J17, J20.0, J20.1, J20.2, J20.3, J20.4, J20.5, J20.6, J20.7, J21.0, J21.1, J21.8, J36, J39.0, J39.1, J69, J85, J86, J94, J95, L0, M0, M01, M03, O, P0, P1, P21, P23, P24, P26, P35.0, P35.1, P35.2, P35.4, P35.4, P36, P37, P50, P51, P54, P75, P76, P77, P78.0, P78.1, P78.2, P78.3, P96.0, R02, R57.2, S, T, V, Z95.8, Z98.2, Z94.8</p>
Type A1 (Hospitalisation caused by SARS-CoV-2 infection)	<p>Not allocated to the types in the rows above, and one of the Covid codes in a primary diagnostic position:</p> <p>U07.1, U07.2, U07.3, U07.4</p>

<p>Type A2 (Hospitalisation suspected to be caused by SARS-CoV-2 infection)</p>	<p>Not allocated to the types in the rows above, Covid Code in a non-primary (U07.1 or U07.2 only) position and/or a Positive Test, as well as codes capturing paediatric symptoms of SARS-CoV-2 infection as the primary reason for admission.</p> <p>These symptoms included: enteritis of unknown cause, unspecified sepsis /viral conjunctivitis, /viral diseases or infections/diarrhoea/infection, coronavirus unspecified, infection associated HLH, volume depletion, shock, otitis media unspecified, coronary artery aneurysm, pulmonary embolism, tachycardias, myocarditis, mesenteric lymphadenitis unspecified, hypotension, unspecified nasopharyngitis/tonsillitis,/pharyngitis, laryngitis/pneumonia/tonsillitis/croup/bronchiolitis/bronchitis, ARDS, pneumothorax, respiratory failure, gastritis unspecified, pain in joints, unspecified acute renal failure, neonatal respiratory issues with air leak, neonatal poor feeding, cough, wheeze, sore throat, abdominal pain, vomiting, unspecific rash, abnormal movements, somnolence, disorientation, dizziness, anosmia, fever, headache, myalgia, malaise, syncope, febrile convulsion, shock, lymphadenopathy, feeding difficulties, unknown cause, abnormal respiratory exam, SARS unspecified .</p> <p>A08.4, A08.3, A08.5, A09.0, A09.9, A41.9, B30.9, B33.8, B34.8, B34.9, B97.2, B99, D76.2, E86, G25.9, H66.9, I25.4, I26, I40, I41, I42, I46, I47, I88.0, I95, J00, J01, J02.9, J03.9, J04, J05, J06, J18, J22, J40, J80, J81, J93, J96, J98, K29.7, M25.5, N17.9, P25, P92, R00, R05, R06, R07, R09.8, R10, R11, R13, R21, R29.8, R34, R40, R41, R42, R43, R50, R51, R52, R53, R55, R56, R57, R59, R63.0, R63.3, R63.4, R63.6, R63.8, R68.1, R69, R84.5, U04.9</p> <p>Exclude specific infections that might be alternative causes (primary or non-primary code position): A01, A02, A03, A04, A05, A06, A06, A07, A08.0, A08.1, A08.2, B25, B27, J0.20, J0.30, J09, J10, J11, J12, J13, J14, J15, J16, J17, J20.0, J20.1, J20.2, J20.3, J20.4, J20.5, J20.6, J20.7, J21.0, J21.1</p>
<p>Type B1 (Hospitalisation with SARS-CoV-2 as a contributor alongside other acute conditions)</p>	<p>Not allocated to the types in the rows above, Covid Code in a non-primary position and/or a Positive Test, and one of the following diagnoses as a reason for admission:</p> <p>RSV, adenovirus, staphylococcal pneumonia, streptococcal pneumonia. Conditions that have been linked to SARS-COV-2 infection appendicitis, type one diabetes, status epilepticus or febrile seizures. Treatment codes such as isolation in cubicle.</p> <p>A01, A02, A03, A04, A05, A06, A06, A07, A08.0, A08.1, A08.2, A40, A41, A48.3, A49, A81.8, A85.8, A86, A87.9, A87.0, A87.8, A89, B09, B25, B27, B34, B95, B96, B97, E10, E87.8, G41, I30, I32, J02, J03, J09, J10, J11, J12, J13, J14, J15, J16, J17, J20, J21, J3, J85, J86, J90, K85.9, M30.3, P22, P23, P28, P29, P74, R17, R65, R70, R71, R72, R73, R74, R79, U07.5, Z03.8, Z03.9</p>
<p>Type B2 (Hospitalisation with SARS-CoV-2 as a contributor alongside an underlying health condition)</p>	<p>Not allocated to the types in the rows above, Covid Code in a non-primary position and/or a Positive Test, and one of the following diagnoses as the primary reason for admission:</p> <p>Conditions treated with immune suppression, cancer, neurodevelopmental conditions including those that may affect breathing, endocrine disorders, neonatal conditions such as jaundice or poor feeding, respiratory diseases such as asthma and cystic fibrosis, blood disorders that can affect breathing or cause immune suppression, congenital anomalies that affect the whole body, may impair the heart or circulation or immunity or endocrine function.</p> <p>B20, B21, B22, B24, D3, C, D0, D37, D38, D39, D4, D55, D56, D57, D58, D59, D60, D61, D64.0, D64.4, D66, D67, D68.0, D68.1, D68.2, D70, D71, D72.0, D73.0, D73.1, D76.1, D76.3, D8, E00, E10, E11, E12, E13, E14, E20, E21, E22, E23, E24, E25, E26, E27, E4, E6, E7, E80, E83, E84, E85, E88, E89, F72, F73, F78, F79, F83, F84, F88, F89, G1, G20, G21, G22, G23, G24, G3, G40, G45, G46, G47, G7, G8, G91, G94, I05, I06, I07, I08, I09, I10, I11, I12, I13, I15, I27, I28, I31, I34, I35, I36, I37, I42, I43, I44, I45, I47, I48, I49, I50, I51, I52, J38.0, J38.6, J41, J42, J43, J44, J45, J46, J47, J82, J84, J98.4, J99, K44, K50, K51, K52, K71, K72, K73, K74, K75, K76, K90, L1, L85, L93, L94, M05, M06, M07, M08, M09, M30.0, M30.1, M30.2, M31, M32.1, M32.8, M32.9, M33, M34, M35, M41, M42, M43, N0, N11, N12, N13, N15, N18, N19, P05, P07, P27, Q0, Q2, Q30, Q31, Q32, Q33, Q34, Q35, Q36, Q37, Q39, Q4, Q60, Q61, Q62, Q63, Q64, Q65, Q67, Q75, Q76, Q77, Q78, Q79, Q80, Q81, Q85, Q87, Q89, Q90, Q91, Q92, Q93, R16, R62, R56.8, R94</p>

Demographics

Age will be grouped as < 1 (i.e., Infants), 1 - 4, 5 - 11, 12 - 15, and 16 - 17 years, sex, ethnicity (coded via adapted ONS data dictionary): Asian / Asian British, Black / Black British, Chinese, Mixed, Other, Unknown, White), socioeconomic deprivation information derived by mapping patients' Lower Layer Super Output Areas (LSOA) to the English Index of Multiple Deprivation (IMD)²⁹; reported as quintiles.

Pre-existing health conditions

As detailed in Table 3 we will identify two groups of medical and developmental underlying health conditions given their importance as risk factors for severe disease with SARS-CoV-2.^{16, 21, 23, 30, 31}

a) Pre-existing conditions recognised by the English Vaccination Programme

The Joint Committee for Vaccination and Immunisation (JCVI) of England identified certain health conditions as placing children at greater vulnerability of severe disease with SARS-CoV-2 infection, these are listed in the 'Green Book'.³² Only groups listed in this guidance are offered Covid-19 vaccination from the age of 6 months.⁸ As previously described,² the relevant conditions³² were matched to ICD-10¹⁹, and children and adolescents with any evidence of these conditions in hospital episode statistics (either outpatient or inpatient) were identified.

b) A broader list of pre-existing, medical and developmental health conditions

As previously described,² based on clinical consensus, using ICD-10 codes, we will identify a wider group of medical and developmental health conditions representing all conditions that appeared in our original cohort study, in the hospital records of children with SARS-CoV-2 associated hospitalisation prior to their date of infection; we defined criteria for

obesity based on weight-for-age and sex standard deviation score (SDS);³³ and World Health Organisation standards³⁴; we define pregnancy via the presence of associated ICD-10 codes within a 9-month time window to the date of infection.

Table 3: ICD-10 codes defining conditions associated with clinical vulnerability and other medical and developmental health conditions linked to SARS-CoV-2 associated hospitalisation

ICD-10 match to conditions specifically lagged by JCVI as leading to greater vulnerability to severe disease with SARS-CoV-2 https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a	ICD-10 Codes presented in the format provided by the World Health Organisation 2019: https://icd.who.int/browse10/2019/en Where we present a code as a single letter, then we include the whole chapter (eg: C); where we present a code as a letter with a single number (eg: C0) we include all codes starting with this letter number combination; where we present a code as a letter with two numbers (eg: C00) we include all codes starting with this letter number combination; and where we present a code with a letter and three numbers with a decimal point (eg: C00.0) we include only this specific code.
Cancer excluding benign tumours, (only considered within 5 years prior to appearance in cohort)	C, D0
Blood Disorders and Immune Deficiencies	B20, B21, B22, B24, D56, D57, D58, D61, D71, D72.0, D73.0, D73.1, D8
Endocrine Conditions	E10, E11, E12, E13, E14, E22, E23, E24, E25, E26, E27, E70, E71, E72, E74, E75, E76, E79, E84
Severe Neurological and Developmental Conditions	F72, F73, F84, G1, G20, G21, G22, G23, G24, G26, G3, G40, G45, G7, G8
Hypertension, Cardiac Valves and Cardiomyopathy	I10, I11, I12, I13, I15, I27, I34, I35, I36, I37, I42, I43
Severe Respiratory Diseases	B27 (only considered in the prior 5 years), J38.0, J38.6, J44, J45, J46, J47, J82, J84, J99
Digestive, Liver and Renal Diseases	K44, K50, K51, K71, K72.1, K74.0, K74.1, K74.4, K74.5, K75, N03, N04, N18.3, N18.4, N18.5
Arthritis and Connective Tissue Diseases	M05, M06, M07, M08, M09, M30.0, M30.1, M30.2, M31, M32.1, M34, M35
Certain Congenital Syndromes and Anomalies affecting heart lungs kidneys liver or multi-system	Q0, Q20, Q21.0, Q21.2, Q21.3, Q21.4, Q21.8, Q22, Q23, Q24.2, Q24.4, Q24.5, Q24.6, Q25, Q26, Q31, Q32, Q33, Q34, Q39, Q44.2, Q60, Q61, Q79, Q80, Q81, Q897, Q9
Obesity if over the age of 16 years	E66
Pregnancy (only considered up to nine months prior to appearance in cohort)	O

Medical and developmental UHC (a wider selection based on consultant paediatrician views)	ICD-10 Codes
Cancer and Neoplasms excluding benign tumours, (only considered within the prior 5 years)	C, D0, D37, D38, D39, D4
Blood Disorders and Immune Deficiencies	B20, B21, B22, B24, D55, D56, D57, D58, D59, D60, D61, D64.0, D64.4, D66, D67, D68.0, D68.1, D68.2, D70, D71, D72.0, D73.0, D73.1, D76.1, D76.3, D8, R16
Endocrine Conditions	E00, E10, E11, E12, E13, E14, E20, E21, E22, E23, E24, E25, E26, E27, E3, E4, E6, E7, E80, E83, E84, E85, E88, E89
Neurological and Developmental Conditions	F72, F73, F78, F79, F83, F84, F88, F89, G1, G20, G21, G22, G23, G24, G3, G40, G45, G47, G5, G6, G7, G8, G91, G94, P21, Q0, Q1, Q90, Q91, Q92, Q93, R56.8, R62, R94
Respiratory Conditions	B27 (only considered in the prior 5 years), J38.0, J38.6, J41, J42, J43, J44, J45, J46, J47, J82, J84, J98.4, J99, Q30, Q31, Q32, Q33, Q34
Congenital Heart Disease, Hypertension and Acquired Heart disease	I05, I06, I07, I08, I09, I10, I11, I12, I13, I15, I27, I28, I31, I34, I35, I36, I37, I42, I43, I44, I45, I47, I48, I49, I50, I51, I52, Q2
Digestive and Liver Conditions	K44, K50, K51, K71, K72.1, K74.0, K74.1, K74.4, K74.5, K74.6, K75, K76, K90, Q35, Q36, Q37, Q39, Q4
Muscle, Skin and Arthritis	L1, L85, L93, L94, M05, M06, M07, M08, M09, M30.0, M30.1, M30.2, M31, M32.1, M32.8, M32.9, M34, M35, M41, M42, M43, Q65, Q67, Q71, Q72, Q73, Q74, Q75, Q76, Q77, Q78, Q79, Q80, Q81, Q85, Q87, Q89
Renal and Genitourinary Conditions	N0, N11, N12, N13, N15, N18, N31, N32, Q5, Q60, Q61, Q62, Q63, Q64
Prematurity and Low Birth Weight, (only considered within the prior 5 years)	P05, P07

Time eras for SARS-CoV-2 variants

We will assign a dominant SARS-CoV-2 variant to each admission using the following time

eras: Original variant: 1st July 2020 to 7th December 2020 (5-months, 1-week); Alpha variant:

8th December 2020 to 17th May 2021 (7-months, 1-week); Delta variant 18th May 2021 to

13th December 2021 (7-months), Omicron variant 14^h December 2021 to 30th September

2023 divided into three 7-month blocks to illustrates trends over this era.³⁵

Vaccination status

Vaccination status will be coded as “unvaccinated”, or first, second or third/booster dose

(“vaccinated”) determined by the number of vaccinations received 14 days prior to

admission. Vaccine type was not reported as only Pfizer-BioNTech COVID-19 vaccine (Comirnaty) is approved for paediatric use in England.

Descriptive statistics

The protocol, the phenotyping and analysis code are saved

(https://github.com/BHFDSC/CCU029_02).

We will describe hospital admissions that were caused or contributed to by SARS-CoV-2 infection, stratified by the admission type over the study period. We will define severe outcomes as: SARS-CoV-2 associated hospital admission involving paediatric critical care and/or due to MIS-C, as specified by the UK Joint Committee for Vaccination and Immunisation (JCVI).^{36, 37} Amongst the children and adolescents with SARS-CoV-2 related hospitalisation, we will calculate the proportions in each of the 6 defined variant associated time eras over the study period (Original, Alpha, Delta and Omicron time periods), by hospital admission types and, by patient characteristics. We will explore temporal trends in the proportion of hospital admissions with each factor of interest, by fitting a linear regression model to the 6 serial period proportions (each representing a time-period) and we will report the associated slope parameter p-value. We will summarize characteristics by era for brevity, by reporting variables summarised by grouped eras of pre-Omicron (19.5 months) versus Omicron (21 months) using a chi square test.

References

1. ONS. Interactive Population Pyramid. Accessed 20 October, 2021.
<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/ukpopulationpyramidinteractive/2020-01-08>
2. Wilde H, Tomlinson C, Mateen BA, et al. Hospital admissions linked to SARS-CoV-2 infection in children and adolescents: cohort study of 3.2 million first ascertained infections in England. *BMJ*. Jul 5 2023;382:e073639. doi:10.1136/bmj-2022-073639
3. Buonsenso D, Cusenza F, Passadore L, Bonanno F, De Guido C, Esposito S. Duration of immunity to SARS-CoV-2 in children after natural infection or vaccination in the omicron and pre-omicron era: A systematic review of clinical and immunological studies. *Front Immunol*. 2022;13:1024924. doi:10.3389/fimmu.2022.1024924
4. Soriano-Arandes A, Brett A, Buonsenso D, et al. Policies on children and schools during the SARS-CoV-2 pandemic in Western Europe. *Front Public Health*. 2023;11:1175444. doi:10.3389/fpubh.2023.1175444
5. ONS. Coronavirus (COVID-19) Infection Survey, UK Statistical bulletins. Office of National Statistics. Updated March 24, 2023. Accessed October 10, 2023.
<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveys/pilot/previousReleases>
6. ONS. COVID-19 Schools Infection Survey, England: pupil antibody data and vaccine sentiment, March to April 2022. Updated 27 June 2022. Accessed Oct 10, 2023.
<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/covid19schoolsinfectionsurveyengland/pupilantibodiesandvaccinesentimentmarch2022>

7. UK-GOV. Coronavirus data: vaccination rates. UK-Gov. Accessed Nov 1, 2023.
<https://api.coronavirus.data.gov.uk/v2/data?areaType=nation&areaCode=E92000001&metric=vaccinationsAgeDemographics&format=csv>
8. NHSE. Covid-19 Vaccination. NHSE. October 10, 2023. Accessed October 10, 2023.
<https://www.nhs.uk/conditions/covid-19/covid-19-vaccination/getting-a-covid-19-vaccine/>
9. Holm M, Espenhain L, Glenthøj J, et al. Risk and Phenotype of Multisystem Inflammatory Syndrome in Vaccinated and Unvaccinated Danish Children Before and During the Omicron Wave. *JAMA Pediatr.* Jun 8 2022;doi:10.1001/jamapediatrics.2022.2206
10. Iuliano AD, Brunkard JM, Boehmer TK, et al. Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods - United States, December 2020-January 2022. *MMWR Morb Mortal Wkly Rep.* Jan 28 2022;71(4):146-152. doi:10.15585/mmwr.mm7104e4
11. Buonsenso D, Perramon A, Catala M, et al. Multisystem Inflammatory Syndrome in Children in Western Countries? Decreasing Incidence as the Pandemic Progresses?: An Observational Multicenter International Cross-sectional Study. *The Pediatric infectious disease journal.* Dec 1 2022;41(12):989-993. doi:10.1097/INF.0000000000003713
12. NHS. Paediatric Critical Care Minimum Dataset. Accessed Jan 4, 2023.
https://www.datadictionary.nhs.uk/data_sets/supporting_data_sets/paediatric_critical_care_minimum_data_set.html
13. Wood A, Denholm R, Hollings S, et al. Linked electronic health records for research on a nationwide cohort of more than 54 million people in England: data resource. *BMJ.* Apr 7 2021;373:n826. doi:10.1136/bmj.n826
14. ONS. Single year of age and average age of death of people whose death was due to or involved coronavirus (COVID-19). UK Government Accessed Nov 1, 2023.

<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/singleyearofageandaverageageofdeathofpeoplewhosedeadwasduetoorinvolvedcovid19>

15. Ward JL, Harwood R, Smith C, et al. Risk factors for PICU admission and death among children and young people hospitalized with COVID-19 and PIMS-TS in England during the first pandemic year. *Nat Med*. Dec 20 2021;doi:10.1038/s41591-021-01627-9
16. Smith C, Odd D, Harwood R, et al. Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. *Nat Med*. Jan 2022;28(1):185-192. doi:10.1038/s41591-021-01578-1
17. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. May 23 2020;395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1
18. Bhattacharya A, Collin SM, Stimson J, et al. Healthcare-associated COVID-19 in England: A national data linkage study. *J Infect*. Nov 2021;83(5):565-572. doi:10.1016/j.jinf.2021.08.039
19. WHO. ICD-10 Version 2019. June 6, 2022. Accessed June - December, 2022. <https://icd.who.int/browse10/2019/en#/V>
20. Swann OP, L. Holden, K.A et al. Comparison of children and young people admitted with SARS-CoV-2 across the UK in the first and second pandemic waves: prospective multi centre observational study. Pre Print. 2021;
21. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. Aug 27 2020;370:m3249. doi:10.1136/bmj.m3249

22. Swann O, Pollock, L., Holden, KA. et al. Comparison of children and young people admitted with SARS-COV-2 across the UK in the first and second pandemic waves. 2021. Paper prepared by the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) for SAGE. 2021. <https://www.gov.uk/government/publications/isaric-comparison-of-children-and-young-people-admitted-with-sars-cov-2-across-the-uk-in-the-first-and-second-pandemic-waves-prospective-multicentr>
23. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr.* Sep 1 2020;174(9):868-873.
doi:10.1001/jamapediatrics.2020.1948
24. Frost HM, Sebastian T, Keith A, et al. COVID-19 and Acute Otitis Media in Children: A Case Series. *J Prim Care Community Health.* Jan-Dec 2022;13:21501319221082351.
doi:10.1177/21501319221082351
25. Sedighi I, Fahimzad A, Pak N, et al. A multicenter retrospective study of clinical features, laboratory characteristics, and outcomes of 166 hospitalized children with coronavirus disease 2019 (COVID-19): A preliminary report from Iranian Network for Research in Viral Diseases (INRVD). *Pediatr Pulmonol.* Feb 2022;57(2):498-507.
doi:10.1002/ppul.25756
26. Marks KJ, Whitaker M, Agathis NT, et al. Hospitalization of Infants and Children Aged 0-4 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 2020-February 2022. *MMWR Morb Mortal Wkly Rep.* Mar 18 2022;71(11):429-436.
doi:10.15585/mmwr.mm7111e2

27. Rouva G, Vergadi E, Galanakis E. Acute abdomen in multisystem inflammatory syndrome in children: A systematic review. *Acta Paediatr.* Mar 2022;111(3):467-472.
doi:10.1111/apa.16178
28. Kanthimathinathan HK, Buckley H, Davis PJ, et al. In the eye of the storm: impact of COVID-19 pandemic on admission patterns to paediatric intensive care units in the UK and Eire. *Crit Care.* Nov 17 2021;25(1):399. doi:10.1186/s13054-021-03779-z
29. ONS. Populations by Index of Multiple Deprivation (IMD) decile, England and Wales, 2020. Updated Oct 2021. Accessed Jan 5, 2023.
<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/adhocs/13773populationsbyindexofmultipledeprivationimddecileenglandandwales2020>
30. Antoon JW, Grijalva CG, Thurm C, et al. Factors Associated With COVID-19 Disease Severity in US Children and Adolescents. *J Hosp Med.* Oct 2021;16(10):603-610.
doi:10.12788/jhm.3689
31. Bundle N, Dave N, Pharris A, et al. COVID-19 trends and severity among symptomatic children aged 0-17 years in 10 European Union countries, 3 August 2020 to 3 October 2021. *Euro Surveill.* Dec 2021;26(50)doi:10.2807/1560-7917.ES.2021.26.50.2101098
32. UKHSA. Coronavirus (COVID-19) vaccination information for public health professionals Chapter 14a. Updated September 2022 Accessed Jan 5 2023.
<https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a>
33. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med.* Feb 28 1998;17(4):407-29.

34. WHO. Obesity and overweight. WHO. Accessed May 20, 2022.
<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
35. COG-UK. Sars2. <http://sars2.cvr.gla.ac.uk/cog-uk/>
36. JCVI. JCVI statement on vaccination of children aged 5 to 11 years old. GOV.UK. .
Accessed July 24, 2022. <https://www.gov.uk/government/publications/jcvi-update-on-advice-for-covid-19-vaccination-of-children-aged-5-to-11/jcvi-statement-on-vaccination-of-children-aged-5-to-11-years-old>
37. JCVI. JCVI statement on vaccination of children aged 12 to 15 years old. GOV.UK.
Accessed July 24, 2022. <https://www.gov.uk/government/publications/jcvi-statement-september-2021-covid-19-vaccination-of-children-aged-12-to-15-years/jcvi-statement-on-covid-19-vaccination-of-children-aged-12-to-15-years-3-september-2021>