Hospitalizations and Paediatric Intensive Care Admissions due to COVID-19 and PIMS-TS among Children and Young People in England over 2 years, Feb 2020 – Jan 2022

Joseph L Ward PhD,[1] Rachel Harwood PhD,[2] Simon Kenny MD,[2,3] Joana Cruz PhD,[1] Matthew Clark MB BChir,[3] Peter J Davis FRCPCH,[4] Elizabeth S Draper PhD,[5] Dougal Hargreaves MD(Res),[6] Shamez Ladhani PhD,[7] Nick Gent PhD,[7] Hannah Williams PhD,[7] Karen Luyt PhD,[8] Steve Turner MD,[9,10] Elizabeth Whittaker PhD,[10] Alex Bottle PhD[6], Lorna K Fraser PhD,[11] Russell M Viner PhD [1]

Affiliations

1: UCL Great Ormond St. Institute of Child Health, London

2: Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool

3: NHS England and Improvement

4: Paediatric Intensive Care Unit, Bristol Royal Hospital for Children, Bristol

5: PICANet, Department of Health Sciences, University of Leicester, Leicester

6: Imperial College London, Department of Primary Care and Public Health

7. UK Health Security Agency

8 Bristol Medical School, University of Bristol, Bristol

9. NHS Grampian

10. Imperial College School of Medicine, London

11. Martin House Research Centre, Dept of Health Sciences, University of York

Correspondence:

Dr. Joseph Ward

UCL Great Ormond St. Institute of Child Health

30 Guilford St. London WC1N 1EH

Joseph.ward@ucl.ac.uk

Word 3298

Hospitalizations and Paediatric Intensive Care Admissions due to COVID-19 and PIMS-TS among Children and Young People in England Feb 1st 2020 – Jan 31st 2022

Abstract

Importance

Investigating how risks of serious illness after SARS-CoV-2 infection in children and young people (CYP) have changed as new variants have emerged, is essential to inform public health interventions and clinical guidance as the pandemic progresses.

Objective

Here we examine total hospitalizations, paediatric intensive care unit (PICU) admissions and deaths in England amongst CYP aged 0-17 after hospitalization for COVID-19 and Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 during the first two years of the pandemic. We assess if risk factors for serious illness have changed with the emergence of SARS-CoV-2 variants

Design

Population level analysis of hospitalizations after SARS-CoV2- infection in England amongst CYP from 1st Feb 2020 to 31st Jan 2022

Setting

Analysis of national data on hospital activity amongst CYP in England, linked with data on SARS-CoV-2 testing data, SARS-CoV-2 vaccination data, PICU admissions, and mortality.

Participants

CYP aged 0-17 hospitalized in England with COVID-19 or PIMS-TS.

Exposures

Previous medical comorbidities, sociodemographic factors and timing of hospitalization when different SARS-CoV-2 variants were dominant in England (Wild-type, Alpha, Delta and Omicron).

Main outcomes

Paediatric intensive care admission and death within 28 days of hospitalization with COVID-19 or PIMS-TS.

Results

We identified 10,540 hospitalizations due to COVID-19 and 997 due to PIMS-TS, within 1,125,010 emergency hospitalizations for other causes. The number of hospitalizations due to COVID-19 and PIMS-TS per new SARS-CoV-2 infections in England declined during the second year of the pandemic. Within hospitalized CYP, 4.3% required PICU admission due to COVID-19, declining from 9.9% with Wild Type, 6.1% with Alpha, 3.4% with Delta to 1.7% with Omicron. 48 CYP died within 28 days of hospitalization due to COVID-19, and none from PIMS-TS (PIMS-S data were limited to November 2020 onwards). Risk of severe COVID-19 in CYP was associated with medical comorbidities, regardless of SARS-CoV-2 variant. Results were similar when CYP with prior exposure to SARS-CoV-2 or vaccination were excluded.

Conclusion

The risk of severe disease from SARS-CoV-2 infection in CYP in England remained low across the first two years of the pandemic. CYP with multiple medical problems and particularly neurodisability should be central to vaccination and public health measures as further variants emerge.

Key points

Question

What are the risks of serious SARS-CoV-2 infection amongst children and young people (CYP) and have these changed as new variants have emerged?

Findings

In this population level analysis of hospitalizations with COVID-19 and PIMS-TS amongst CYP in England, risk of intensive care admission and death remained very low across the first two years of the pandemic, and decreased as new variants emerged. CYP with complex medical problems and neurodisability were most vulnerable, regardless of SARS-CoV-2 variant.

Meaning

These data provide further reassurance regarding the risk of severe illness after SARS-CoV-2 infection in CYP, but also highlight how CYP with neurodisability should be central to vaccination and public health interventions as the pandemic progresses.

Hospitalizations and Paediatric Intensive Care Admissions due to COVID-19 and PIMS-TS among Children and Young People in England Feb 1st 2020 – Jan 31st 2022

Introduction

Evidence from the first COVID-19 pandemic year show that the majority of children and young people (CYP) develop a mild illness following SARS-CoV-2 infection, and that serious outcomes are rare.[1-4] However, as new SARS-CoV-2 variants have emerged, additional data on risk of severe disease are needed to inform clinical and public health responses as the pandemic progresses.[5-8]

Assessing the severity of different SARS-CoV-2 variants is complex, and dependent on multiple factors which may vary by age.[9,10] These include immunity from prior infection, patterns of healthcare utilization, changes to shielding advice, and eligibility and effectiveness of vaccination.

An increase in hospitalizations amongst CYP with the Delta (B.1.617.2) variant in summer 2021, and particularly after the emergence of the Omicron (B.1.1.529) variant in December 2021,[7,8] led to concerns CYP may have become more vulnerable to serious disease. However, rise in hospitalizations may reflect variation in community infection rates[7,11] and higher incidental infections among hospitalised CYP, rather than more severe disease.[12,13] Although monitoring hospitalisations is critical for COVID-19 surveillance in CYP, we must also examine other indicators of disease severity, such hospitalizations requiring paediatric intensive care unit (PICU) admission, and deaths.

Previous work assessing severity across different SARS-CoV-2 variants amongst CYP has been based on notification systems within hospitals or on limited regional data, and are open to bias. National population-level analyses are lacking for more recent variants.[8,14,15] Here we use a unique dataset including all hospitalizations amongst CYP aged 0-17 in England linked to national data on SARS-CoV-2 testing, SARS-CoV-2 vaccination, PICU admissions, and deaths. We describe numbers of hospitalizations, PICU admissions and deaths after hospitalization for both COVID-19 and Paediatric Inflammatory Multisystem Syndrome

Temporally Associated with SARS-CoV-2 [14], and assess if previously identified risk factors for serious illness have changed with the emergence of different variants.

Methods

Data

We used Secondary Use Services (SUS) data provided by NHS England, a dataset covering 98% of national inpatient activity. We analysed all hospitalizations in England within 0-17 year olds from Feb 1st 2020 to Jan 31st 2022. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.[16]

Hospitalization data were deterministically linked with the following English national datasets: 1) all community and hospital-based PCR and lateral flow tests for SARS-CoV-2 provided by the UK Health Security Agency (UKHSA); 2) data on all UK PICU admissions provided by the Paediatric Intensive Care Audit Network (PICANeT); 3) death registrations provided by the Office for National Statistics (ONS); 4) death notifications provided by the National Child Mortality Database (NCMD); and 5) SARS-CoV-2 vaccination data provided by UKHSA. We also obtained authoritative modelled monthly estimates of new infections with SARS-CoV-2 in under 18 year-olds by age group in England from UKHSA.[17,18]

Outcomes

We used PICU admission after hospitalization with COVID-19 or PIMS-TS as our main indicator for severe SARS-CoV-2 infection. We also examined deaths within 28 days of hospitalization with COVID-19 or PIMS-TS from death registration data (excluding deaths due to injury), or notification data within the NCMD, to account for delay in death registration.[19] Note NCMD data were only available to the end of November 2021, and underlying cause of death was not available in these data.

Exposures

Reason for Hospitalization

We defined COVID-19 hospitalizations as those where the primary reason for hospitalization was recorded using an ICD-10 COVID-19 code (UO71, UO72, UO73, UO74). This highly specific definition (hereafter "Primary COVID-19") may miss cases where the diagnosis was unclear, or among CYP with multiple medical problems. To account for this, we also identified hospitalizations where a COVID-19 code was recorded as either the primary or secondary diagnosis, or where the CYP had a positive PCR or lateral flow test for SARS-CoV-2 within 7

days of admission or discharge. This definition (hereafter "Primary/Secondary COVID-19") is likely to be highly sensitive, but will capture hospitalisations for other reasons, including incidental SARS-CoV-2 infections. We defined hospitalizations due to PIMS-TS where the relevant ICD-10 code (UO75) was the primary reason for admission, as this condition was unlikely to be recorded as a secondary diagnosis due to its severity. This code was introduced in November 2020, and so we restricted this analysis to Nov 1st 2020- Jan 31st 2022. For all definitions, we excluded elective and maternal hospitalizations, and those where the primary reason for admission was an injury (ICD 10 chapters 19 and 20).

Variants of concern

We defined time periods where different variants were dominant in England using UKHSA data as: Wild-type 1st Feb 2020 to 30th Jan 2021; Alpha 31st Jan 2021 to 15th May 2021; Delta 16th May 2021 to 11th Dec 2022; Omicron 12th December 2021 to 31st Jan 2022.

Co-morbidities and sociodemographic factors

We used hospitalization data from 1st March 2015 onwards to identify medically recorded co-morbidities in CYP and to populate sociodemographic variables. We grouped comorbidity diagnoses by body system and identified CYP with life-limiting conditions using established code lists.[20,21] We categorised age as: 0-4, 5-11 and 12-17 years, and ethnicity as: White, Mixed, Asian, Black, Other and unknown. We used Index of Multiple Deprivation (IMD) 2019 quintile category (hereafter IMD category) to define area level socioeconomic status.

Analyses

We describe hospitalizations with COVID-19 and PIMS-TS by sociodemographic factors and previous comorbidities, and examine hospitalizations per 100,000 monthly new infections with SARS-CoV-2 in England. We then examine differences in sociodemographic characteristics of hospitalizations with dominant SARS-CoV-2 variants using standardized residuals from chi^2 statistics.

We describe numbers of hospitalized CYP with COVID-19 and PIMS-TS who were admitted to PICU, or died within 28 days of hospitalisation. We then repeated this amongst CYP with and without prior exposure to infection or vaccination. We considered CYP to have been infected

with SARS-CoV-2 from the date of first positive SARS-CoV-2 test or hospitalization with either Primary or Secondary COVID-19, or PIMS-TS, whichever was sooner. We considered CYP to be vaccinated from 14 days after receiving any SARS-CoV-2 vaccine.

We then modelled the association between sociodemographic factors and presence of co-morbidities among hospitalizations with COVID-19 and PIMS-TS with the odds of PICU admission. We used generalized estimation equations (GEE) to account for multiple admissions within the same CYP, using a logit link and specifying the covariance structure as "exchangeable". We then compared odds ratios and predicted probability for PICU admission during the whole pandemic with those during different variants. We conducted analyses in Stata 16 (StataCorp, College Station TX).

Ethics approval was provided after review by Yorkshire and the Humber, South Yorkshire NHS Research Ethics Committee on 10th June 2021 (Reference 21/YH/0127). Control Of Patient Information (COPI) regulations provided a legal basis for linking these datasets without consent.[22]

Results

Hospitalizations with COVID-19

Between Feb 1st 2020 - Jan 31st 2022, there were 1,125,010 non-traumatic emergency hospitalizations in CYP aged 0-17 in England. Among these, there were 10,540 hospitalizations with Primary COVID-19 among 10,298 CYP. 9827 (93.2%) of these were amongst CYP without prior exposure to SARS-CoV-2 infection or vaccination. There were 33,597 hospitalizations with Primary/Secondary COVID-19 among 29,262 CYP. Patterns of hospitalizations were similar with the two definitions (see eFigure 1). We focus on Primary COVID-19 here with findings for Primary/Secondary COVID-19 shown in supplementary material.

Monthly COVID-19 hospitalizations tracked closely with estimated infections (Figure 1). The highest number of monthly hospitalizations due to Primary COVID-19 was 2,304 in Jan 2022, with 1,631 (71%) of these occurring in CYP aged <5 years. Monthly hospitalizations with Primary COVID-19 per 100,000 infections was highest in May 2020 at 345, with another peak in January 2021 of 219. Monthly hospitalizations per 100,000 new infections were highest and more variable among children aged <5 years, and lowest amongst 5-9 year olds. In 12-17 year-olds, hospitalization rates declined steadily after August 2021 with a small increase in January 2022 (eFigure 3 and 5).

Overall, 54% of hospitalizations for Primary COVID-19 were among males and 62% were CYP aged <5 years old. The age distribution varied over time, with <5 years forming a higher proportion during Omicron than in previous variants. CYP from deprived neighbourhoods and those who were black, Asian or mixed ethnicities were overrepresented in hospitalizations throughout. We identified medical comorbidities in 43.9% of all CYP hospitalized with Primary COVID-19, ranging from 29.1% amongst <5 year-olds to 69.5% amongst 12-17 year-olds (eTable 2).

PICU admissions within 28 days after hospitalization with COVID-19

Overall, 4.3% of Primary COVID-19 hospitalizations required PICU admission, lowest in <5 year-olds (2.2%) compared with 5-11 (7.9%) and 12-17 (7.5%) year-olds (Table 3). The proportion of hospitalizations requiring PICU admission declined as the pandemic progressed, from 9.9% during Wild-type, 6.1% during Alpha, 3.4% during Delta and 1.7% during Omicron

periods, with similar patterns seen in all age-groups. Patterns of PICU admissions and hospitalizations due to Primary COVID-19 were similar amongst CYP without prior exposure to SARS-CoV-2 (eTable 7).

Among CYP with comorbidities hospitalized with Primary COVID-19, 8.6% required PICU admission, compared to 0.9% in CYP without comorbidities (Table 4). This increased from 3.9% in those with comorbidities within 1 body system, to 12.2% for comorbidities in >1 body system, and 17.0% for life-limiting neurodisability. The proportion of CYP requiring PICU admission declined as the pandemic progressed amongst those with and without comorbidities.

After adjusting for the presence of any comorbidity, CYP aged 5-11 and 12-17 had significantly increased odds of PICU admission for Primary COVID-19 compared with <5 year-olds, as did Black, Asian and CYP from ethnic groups not specified compared with white CYP. Associations between sociodemographic factors and odds of PICU admission remained similar across different variants, with older CYP, and those who were Black, Asian or of unknown ethnicity, most at risk. Being in the least deprived quintile of deprivation was associated with increased odds of PICU admission only during the Alpha period. Adjusted odds ratios for PICU admission with Primary COVID-19 associated with comorbidity status by dominant variant are shown in Figure 2. Compared to CYP with no comorbidity, the odds of PICU admission were significantly increased for CYP with any comorbidity (OR 7.66 [5.58-10.49]), with only one body system involved (OR 3.71 [2.56-5.37]), CYP with 2+ body systems involved (OR 11.39 [8.18-15.88]) and CYP with life-limiting neurodisability (OR 15.13 [10.06-22.76]). CYP with any form of comorbidity had higher odds of PICU admission than those without comorbidity across all variants. While odds appeared highest during the Omicron period, confidence intervals were wide and overlapping (eTable 4 and 5).

Hospitalizations with PIMS-TS

Between 1st November 2020 and 31st January 2022 there were 997 hospitalizations with PIMS-TS, (among 961 CYP) of which 928 (93.9%) were amongst CYP without prior SARS-CoV-2 infection or vaccination. The number of hospitalizations per 100,000 SARS-CoV-2 infections was highest during Alpha, peaking at 87.6 in February 2021 (eFigure 4). From May 2021 to the

end of the study period there were under 20 monthly hospitalizations due to PIMS-TS per 100,000 SARS-CoV-2 infections. 62% of hospitalizations with PIMS-TS were amongst males, 59% were amongst CYP aged 5-11, and 29% were amongst CYP aged 12-17 (Table 2). 48% of hospitalizations were amongst white CYP compared with 71% amongst all non-traumatic emergency hospitalizations during this period. There was little change in demographic characteristics of PIMS-TS hospitalizations across dominant variants, although when Alpha was the dominant variant there were higher numbers of CYP aged under 5, lower numbers of CYP who were white and higher numbers of CYP from the most deprived quintile, than were expected. When Omicron was dominant, there were also higher than expected numbers of white CYP, and fewer CYP from the most deprived neighbourhoods. 69.7% of PIMS-TS hospitalizations were among CYP with an identified comorbidity, however a high proportion of these may have been acute complications. After excluding haematological and non-congenital cardiac conditions (common acute manifestations of PIMS-TS) 35.6% of hospitalizations had a previous comorbidity. Further, 546 (54%) of PIMS-TS hospitalizations occurred within CYP who had no previous admissions to hospital recorded in our data (ie since March 2015).

Admissions to PICU within 28 days after hospitalizations with PIMS-TS

Overall 437 (43.8%) of hospitalizations with PIMS-TS required PICU admission, highest amongst 12-17 year olds (46.4%) and lowest amongst under 5 year olds (34.1%). Similar to COVID-19, this proportion declined during the pandemic from 58.8% during Wild-type, to 51.8% during Alpha, 45.3% during Delta and 31.1% during Omicron (Table 3). Patterns of hospitalizations due to PIMS-TS requiring PICU admission were similar when only CYP without prior infection or vaccination were included (eTable 7).

After adjusting for the presence of any comorbidity, female sex was associated with increased odds of PICU admission, as were CYP aged 12-17 compared with those under 5, and Asian CYP compared with white CYP (eTable 6). The odds of PICU admission increased in those with any comorbidity compared with those with no comorbidity (OR 2.07 [1.55-2.78]) and for those with comorbidities in more than one body systems (OR 3.11 [2.23 – 4.33]). These associations of comorbidities with risk of PICU admission were similar across dominant variants (eTable 6).

Deaths

There were 48 CYP who died within 28 days of hospitalization with Primary COVID-19, all of whom had documented comorbidity; 44 (92%) had comorbidities affecting 2 or more body systems and 26 (59%) had life-limiting neurodisability. We did not identify any CYP who died within 28 days after admission with PIMS-TS. Further analysis of deaths was not possible due to very low numbers.

Discussion

We present robust national data on risk factors for hospitalization and severe disease related to SARS-CoV-2 infection during the first 2 years of the COVID-19 pandemic in England. We identified 10,540 hospitalizations with Primary COVID-19 across the study period, of which 4.3% were admitted to PICU. Using a broader more sensitive but less specific Primary/Secondary COVID-19 definition we identified 33,597 hospitalizations, of which 3.1% required PICU admission. Monthly hospitalizations closely tracked community infection rates. Hospitalizations per 100,000 new SARS-CoV-2 infections were highest at the start of the pandemic, with a second peak during Alpha across all age groups. Despite the highest community infection rates being associated with Omicron, rates of hospitalisations and PICU admissions were lowest across all age groups with this variant.

We found that the proportion of CYP with COVID-19 requiring PICU declined steeply since the start of the pandemic across all age groups, despite later higher community infection rates. By the Omicron period, the proportion of CYP admitted to PICU for COVID-19 was 1.7%, and amongst CYP without co-morbidities this was 0.3%. To place this in context, 1.2% of all non-traumatic hospitalizations amongst CYP were admitted to PICU during the study period, and this proportion was 0.9% in the year prior to the pandemic.[3] These falls may reflect multiple mechanisms, including lower disease severity with more recent variants, changes in clinical practice and thresholds for hospitalization and PICU admission as learning occurred across the pandemic, and higher incidental infections in hospitalised CYP at times of high community infection rates.

We found no changes in major medical risk factors associated with severe COVID-19 disease across variants or compared with our previous report from the first pandemic year.[3] The

majority of CYP who required PICU had medical comorbidities, as did all those who died within 28 days of hospitalization for COVID-19. We found deaths after hospitalization to be extremely uncommon in CYP, as we have previously reported,[23] although we acknowledge deaths occurring outside hospital are not included in our dataset.

We found differences in associations of demographic factors with COVID-19 hospitalisations as the pandemic progressed. Risk factors operating early in the pandemic such as older age, non-white ethnicity and lower socio-economic status tended to attenuate across later variants. These findings may reflect differences between variants, but also higher levels of immunity due to prior infection in those at greater risk, as well as impacts of vaccination.[24-26] Vaccination is only likely to have impacted 12-17 year olds in our study, who were eligible for vaccination in the UK from September 2021, with younger children only included after January 2022. Of note, almost all hospitalized CYP included in our study had no prior exposure to SARS-CoV-2 infection or vaccination.

The pattern of decline in the proportion of hospitalizations requiring PICU admission across the pandemic was also found for PIMS-TS, and we identified no deaths within 28 days of hospitalization after November 2020. This likely reflects changes in clinical practice as knowledge and experience have increased. Further, we found a steep decline in the number of monthly hospitalizations with PIMS-TS per 100,000 SARS-CoV-2 infections after the Alpha period, and no evidence of an increase as subsequent variants emerged. This is consistent with regional data from the UK and elsewhere showing the incidence of PIMS-TS to have reduced during Omicron and Delta compared with Alpha.[14,27]

Our results support previous findings showing low overall risk of serious outcomes after SARS-CoV-2 infection in CYP[3,23] and that disease severity has declined during the pandemic.[7,15] Wan and colleagues reported a lower risk of emergency department attendance, hospitalization, and intensive care support in children aged <5 infected with Omicron compared with Delta in the US.[15] Similarly, Swann et al found severity amongst CYP hospitalized with COVID-19 across the UK to have declined during Alpha compared with early months of the pandemic.[8] An analysis of deaths in CYP in England between March 2020 – December 2021 found 81 to be

due to COVID-19 (1.2% of all deaths over this period), with lower infection fatality rates during Delta than for Alpha or Wildtype.[4]

Strengths and weaknesses

We used multiple linked national datasets to describe COVID-19 and PIMS-TS hospitalizations during the first two years of the pandemic, providing a robust analysis of risks of serious disease not possible with regional or hospital datasets.

Limitations include variable diagnostic coding within SUS, and challenges in identifying true COVID-19 hospitalizations from incidental or past infection. Further, although SARS-CoV-2 testing of all emergency hospitalizations was introduced from the end of April 2020, limited testing availability earlier in the pandemic may have affected identification of COVID-19 hospitalizations, and CYP with multiple comorbidities may have been more likely to have been tested.[28] The ICD-10 code for PIMS-TS cases was only introduced in November 2020 and we did not attempt to examine hospitalizations prior to this using proxy codes. We used chronic condition codes described by Hardelid et al[20] recorded from 2015 to identify CYP with comorbidities. These may have also captured acute complications of PIMS-TS and COVID-19, including within CYP who died. However, as almost all CYP who died had comorbidities in multiple organ systems, and more than half had life-limiting neurodisability, this is unlikely to have substantially affected our results. We found odds of PICU admission with COVID-19 increased with age, but did not specifically examine risks in infants and neonates, and further population-level analyses to explore this are required.[29] We considered COVID-19 admissions to be due to variants which were dominant in England at that time but were unable to confirm this. We used PICU admission as a proxy for disease severity, but did not have data on the level of intensive support required. Thresholds for PICU admission may have changed during the pandemic, and CYP with complex needs may have been admitted to PICU as a precaution.[3] Our estimate for COVID-19 deaths after hospitalization is likely an overestimate, as we were unable to attribute cause of death in this analysis.[4,23] During the first pandemic year, we identified 29 CYP who died within 28 days of hospitalization with COVID-19, of which 8 were found to be attributable to COVID-19 after case note review.[3] Further, we were unable to exclude deaths due to injury for those only reported through the NCMD, which was also restricted until November 2021.

Conclusion

The risk of severe disease from SARS-CoV-2 infection in CYP in England remained low and decreased across the first two years of the pandemic. CYP with multiple medical problems were most at risk regardless of SARS-CoV-2 variant, and should be central to public health measures as further variants emerge.

Acknowledgements Section

Contributions

We would like to thank the National Child Mortality Database (NCMD); Paediatric Intensive Care Audit Network (PICANet); UK Health Security Agency (UKDSA); NHS Digital, NHS England and NHS Improvement Children and Young People Team, (particularly Sophie Solti, Tiffany Watson-Koszel and, Muhammad Ambia,); for their support in identifying, linking and making the data used in this study available for analysis. We would like to further thank the UKDSA for providing estimates for number of new monthly SARS-CoV-2 infections by age group.

Funding

RH is in receipt of a fellowship from Kidney Research UK (grant number TF_010_20171124). LKF is in receipt of funding from Martin House Children's Hospice (there is no specific grant number for this). RMV is in receipt of a grant from the National Institute of Health Research to support this work (grant number NIHR202322). DH is supported by the National Institute for Health Research (NIHR) through the National School for Public Health Research Programme and the Applied Health Research (ARC) programme for North-West London. Funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data access

JW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Data Sharing Statement

These analyses were undertaken using datasets held by NHS England for the use of ongoing service evaluation, held within the National Commissioning Data Repository. Access to these data at individual level are restricted, as described in data sharing agreements between NHS England and specific data providers, and within in the application for ethical approval provided for this study. Aggregated, non-identifiable data used for this study are provided in the supplementary material.

References

1. Smith, C., *et al.* Deaths in Children and Young People in England following SARS-CoV-2 infection during the first pandemic year: a national study using linked mandatory child death reporting data. (2021).
2. Harwood, R., *et al.* Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. *EClinicalMedicine* **44**, 101287 (2022).
3. Ward, J.L., *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. *Nature medicine*, 1-8 (2021).
4. Bertran, M., *et al.* COVID-19 deaths in children and young people: active prospective national surveillance, March 2020 to December 2021, England. (2022).
5. Bager, P., *et al.* Risk of hospitalisation associated with infection with SARS-CoV-2 lineage B. 1.1. 7 in Denmark: an observational cohort study. *The Lancet Infectious Diseases* **21**, 1507-1517 (2021).
6. Bager, P., Wohlfahrt, J., Rasmussen, M., Albertsen, M. & Krause, T. Hospitalisation associated with SARS-CoV-2 delta variant in Denmark. *The Lancet. Infectious Diseases* (2021).
7. Cloete, J., *et al.* Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B. 1.1. 529) variant wave in South Africa: a multicentre observational study. *The Lancet Child & Adolescent Health* **6**, 294-302 (2022).
8. Swann, O.V., *et al.* Comparison of UK paediatric SARS-CoV-2 admissions across the first and second pandemic waves. *Pediatric Research*, 1-10 (2022).
9. Nyberg, T., *et al.* Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B. 1.1. 529) and delta (B. 1.617. 2) variants in England: a cohort study. *The Lancet* **399**, 1303-1312 (2022).
10. Sigal, A., Milo, R. & Jassat, W. Estimating disease severity of Omicron and Delta SARS-CoV-2 infections. *Nature Reviews Immunology* **22**, 267-269 (2022).
11. Lyngse, F.P., *et al.* Increased transmissibility of SARS-CoV-2 lineage B. 1.1. 7 by age and viral load. *Nature communications* **12**, 1-8 (2021).
12. Zsigmond, B., Breathnach, A.S., Mensah, A. & Ladhani, S.N. Very low rates of severe COVID-19 in children hospitalised with confirmed SARS-CoV-2 infection in London, England". *Journal of Infection* (2022).
13. Thelwall, S., Aiano, F., Harman, K., Dabrera, G. & Ladhani, S.N. Risk of hospitalisation and death in children with SARS-CoV-2 delta (B. 1.612. 2) infection. *The Lancet Child & Adolescent Health* **6**, e16-e17 (2022).
14. Cohen, J.M., Carter, M.J., Ronny Cheung, C., Ladhani, S. & Group, E.P.-T.S. Lower risk of multisystem inflammatory syndrome in children (MIS-C) with the delta and omicron variants of SARS-CoV-2. *Clinical Infectious Diseases* (2022).
15. Wang, L., *et al.* Incidence rates and clinical outcomes of SARS-CoV-2 infection with the Omicron and Delta variants in children younger than 5 years in the US. *JAMA pediatrics* (2022).
16. Von Elm, E., *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *The Lancet* **370**, 1453-1457 (2007).

17. Birrell, P., Blake, J., Van Leeuwen, E., Gent, N. & De Angelis, D. Real-time nowcasting and forecasting of COVID-19 dynamics in England: the first wave. *Philosophical Transactions of the Royal Society B* **376**, 20200279 (2021).
18. Birrell, P., Blake, J. & van Leeuwen, E. COVID-19: nowcast and forecast. (2020).
19. Ward, J.L., Zylbersztejn, A., Hardelid, P. & Viner, R. Delay in death registration among adolescents and young adults in England and Wales. *The Lancet Child & Adolescent Health* (2022).
20. Hardelid, P., Dattani, N. & Gilbert, R. Estimating the prevalence of chronic conditions in children who die in England, Scotland and Wales: a data linkage cohort study. *BMJ open* **4**(2014).
21. Fraser, L.K., *et al.* Rising national prevalence of life-limiting conditions in children in England. *Pediatrics* **129**, e923-e929 (2012).
22. NHS Digital. Control of patient information (COPI) notice. (2021).
23. Smith, C., *et al.* Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. *Nature Medicine* (2021).
24. Marks, K.J., *et al.* Hospitalizations of children and adolescents with laboratory-confirmed COVID-19—COVID-NET, 14 States, July 2021–January 2022. *Morbidity and Mortality Weekly Report* **71**, 271 (2022).
25. Lin, D.-Y., *et al.* Effects of Vaccination and Previous Infection on Omicron Infections in Children. *New England Journal of Medicine* (2022).
26. Powell, A.A., *et al.* Protection against symptomatic disease with the delta and omicron BA. 1/BA. 2 variants of SARS-CoV-2 after infection and vaccination in adolescents: national observational test-negative case control study, August 2021 to March 2022, England. *medRxiv* (2022).
27. Sorg, A., *et al.* SARS-CoV-2 variants and the risk of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 among children in Germany. *Infection*, 1-7 (2022).
28. Thomas, R. All hospital emergency patients to be tested for coronavirus. *Health Service Journal* (2020).
29. Gale, C., *et al.* Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. *The Lancet Child & Adolescent Health* **5**, 113-121 (2021).

Table 1 Demographic characteristics of hospitalizations with Primary Covid-19 by dominant variant

		total		Wildtype			Alpha			Delta			Omicron		
		n	prop	n	%	residual	n	%	residual	n	%	residual	n	%	residual
		10540		1635			1616			3789			3500		
Sex	female	4891	46.4	725	44.3	-1.2	731	45.2	-0.7	1850	48.8	2.2*	1585	45.3	-1.0
	male	5649	53.6	910	55.7	1.1	885	54.8	0.6	1939	51.2	-2.0*	1915	54.7	0.9
Age	Under 5	6546	62.1	923	56.5	-2.9*	988	61.1	-0.5	2153	56.8	-4.1*	2482	70.9	6.6*
	5 to 11 years	1807	17.1	324	19.8	2.6*	264	16.3	-0.8	617	16.3	-1.3	602	17.2	0.1
	12 to 17 years	2187	20.7	388	23.7	2.6*	364	22.5	1.6	1019	26.9	8.3*	416	11.9	-11.5*
Ethnicity	White	6580	62.4	905	55.4	-3.6*	926	57.3	-2.6*	2463	65.0	2.0*	2286	65.3	2.2*
	Black	602	5.7	120	7.3	2.8*	100	6.2	0.8	198	5.2	-1.3	184	5.3	-1.1
	Asian	1656	15.7	346	21.2	5.6*	304	18.8	3.1*	523	13.8	-3.0*	483	13.8	-2.9*
	Mixed	498	4.7	72	4.4	-0.6	77	4.8	0.1	178	4.7	-0.1	171	4.9	0.4
	Other	460	4.4	70	4.3	-0.2	91	5.6	2.4*	151	4.0	-1.1	148	4.2	-0.4
	Unknown / not specified	744	7.1	122	7.5	0.6	118	7.3	0.4	276	7.3	0.5	228	6.5	-1.2
IMD quintile group	most deprived quintile	2685	25.5	441	27.0	1.2	420	26.0	0.4	958	25.3	-0.2	866	24.7	-0.9
	second most deprived	2377	22.6	359	22.0	-0.5	439	27.2	3.9*	819	21.6	-1.2	760	21.7	-1.0
	third most deprived	2081	19.7	334	20.4	0.6	324	20.0	0.3	727	19.2	-0.8	696	19.9	0.2
	fourth most deprived	1895	18.0	288	17.6	-0.3	249	15.4	-2.4*	728	19.2	1.8	630	18.0	0.0
	least deprived	1496	14.2	213	13.0	-1.3	184	11.4	-3.0*	554	14.6	0.7	545	15.6	2.2*
	IMD missing	6	0.1	0	0.0	-1.0	0	0.0	-1.0	<5	.	.	<5	.	.

*indicates significantly higher or lower proportion than expected. Cells with <5 cases are supressed.

Table 2 Demographic characteristics of hospitalizations with primary diagnosis of PIMS-TS by dominant variant

		total		Wildtype			Alpha			Delta			Omicron		
		n	%	n	%	residual	n	%	residual	n	%	residual	n	%	residual
		997	1.00	34			334			340			289		
Sex	female	383	38.4	12	35.3	-0.3	128	38.3	0.0	122	35.9	-0.8	121	41.9	0.9
	male	614	61.6	22	64.7	0.2	206	61.7	0.0	218	64.1	0.6	168	58.1	-0.7
Age	Under 5	123	12.3	<5	.	.	67	20.1	4.0*	30	8.8	-1.8	23	8.0	-2.1*
	5 to 11 years	583	58.5	20	58.8	0.0	180	53.9	-1.1	196	57.6	-0.2	187	64.7	1.4
	12 to 17 years	291	29.2	11	32.4	0.3	87	26.0	-1.1	114	33.5	1.5	79	27.3	-0.6
Ethnicity	White	474	47.5	9	26.5	-1.8	123	36.8	-2.8*	181	53.2	1.5	161	55.7	2.0*
	Black	111	11.1	<5	.	.	48	14.4	1.8	34	10.0	-0.6	25	8.7	-1.3
	Asian	182	18.3	16	47.1	3.9*	79	23.7	2.3*	53	15.6	-1.2	34	11.8	-2.6*
	Mixed	60	6.0	<%	.	.	24	7.2	0.9	24	7.1	0.8	10	3.5	-1.8
	Other	45	4.5	<5	.	.	23	6.9	2.0*	12	3.5	-0.9	9	3.1	-1.1
	Unknown / not specified	125	12.5	<5	.	.	37	11.1	-0.8	36	10.6	-1.0	50	17.3	2.3*
IMD quintile group	most deprived	207	20.8	11	32.4	1.5	88	26.3	2.2*	67	19.7	-0.4	41	14.2	-2.5*
	second most deprived	217	21.8	11	32.4	1.3	82	24.6	1.1	71	20.9	-0.3	53	18.3	-1.2
	third most deprived	194	19.5	7	20.6	0.1	80	24.0	1.9	56	16.5	-1.2	51	17.6	-0.7
	fourth most deprived	187	18.8	<5	.	.	43	12.9	-2.5*	72	21.2	1.0	70	24.2	2.1*
	least deprived	192	19.3	<5	.	.	41	12.3	-2.9*	74	21.8	1.1	74	25.6	2.5*

*indicates significantly higher or lower proportion than expected. Cells with <5 cases are supressed.

Table 3 Hospitalizations and PICU admissions due to Primary COVID-19, Primary/Secondary COVID-19 and PIMS-TS, by age group and dominant variant

		Primary Covid-19			Primary / Secondary Covid-19			PIMS-TS		
		Hospitalized	PICU	%	Hospitalized	PICU	%	Hospitalized	PICU	%
All ages	all admissions	10540	448	4.3	33597	1055	3.1	997	437	43.8
	Wild type	1635	162	9.9	3524	278	7.9	34	20	58.8
	Alpha	1616	98	6.1	5943	239	4.0	334	173	51.8
	Delta	3789	129	3.4	12747	348	2.7	340	154	45.3
	Omicron	3500	59	1.7	11383	190	1.7	289	90	31.1
Under 5	all admissions	6546	141	2.2	16363	432	2.6	123	42	34.1
	Wild type	923	45	4.9	1809	101	5.6	<5	<5	.
	Alpha	988	16	1.6	2823	78	2.8	67	26	38.8
	Delta	2153	44	2.0	5825	144	2.5	30	9	30.0
	Omicron	2482	36	1.5	5906	109	1.8	23	5	21.7
5 to 11 years	all admissions	1807	142	7.9	7899	319	4.0	583	260	44.6
	Wild type	324	57	17.6	708	89	12.6	20	11	55.0
	Alpha	264	37	14.0	1273	78	6.1	180	93	51.7
	Delta	617	40	6.5	2850	105	3.7	196	91	46.4
	Omicron	602	8	1.3	3068	47	1.5	187	65	34.8
12 to 17 years	all admissions	2187	165	7.5	9335	304	3.3	291	135	46.4
	Wild type	388	60	15.5	1007	88	8.7	11	7	63.6
	Alpha	364	45	12.4	1847	83	4.5	87	54	62.1
	Delta	1019	45	4.4	4072	99	2.4	114	54	47.4
	Omicron	416	15	3.6	2409	34	1.4	79	20	25.3

Cells with <5 cases are supressed.

Table 4 Hospitalizations and PICU admissions due to Primary COVID-19 within main comorbidity groups, by age group and dominant variant

		Total			Wild type			Alpha			Delta			Omicron		
		n	PICU	%	n	PICU	%	n	PICU	%	n	PICU	%	n	PICU	%
All ages	all	10540	448	4.3	1635	162	9.9	1616	98	6.1	3789	129	3.4	3500	59	1.7
	no comorbidity	5913	52	0.9	782	20	2.6	841	11	1.3	2146	14	0.7	2144	7	0.3
	any comorbidity	4627	396	8.6	853	142	16.6	775	87	11.2	1643	115	7.0	1356	52	3.8
	one body system	2014	78	3.9	335	29	8.7	327	14	4.3	796	22	2.8	556	13	2.3
	more than one body system	2613	318	12.2	518	113	21.8	448	73	16.3	847	93	11.0	800	39	4.9
	life limiting neurodisability	584	99	17.0	109	24	22.0	95	23	24.2	183	36	19.7	197	16	8.1
Under 5	all	6546	141	2.2	923	45	4.9	988	16	1.6	2153	44	2.0	2482	36	1.5
	no comorbidity	4638	23	0.5	583	8	1.4	672			1549			1834		
	any comorbidity	1908	118	6.2	340	37	10.9	316			604			648		
	one body system	1021	24	2.4	160	8	5.0	169			357			335		
	more than one body system	887	94	10.6	180	29	16.1	147			247			313		
	life limiting neurodisability	244	32	13.1	45			33			76	11	14.5	90	10	11.1
5 to 11	all	1807	142	7.9	324	57	17.6	264	37	14.0	617	40	6.5	602	8	1.3
	no comorbidity	609	12	2.0	102	6	5.9	86	5	5.8	221			200		
	any comorbidity	1198	130	10.9	222	51	23.0	178	32	18.0	396			402		
	one body system	419	26	6.2	78	11	14.1	59	7	11.9	149			133		
	more than one body system	779	104	13.4	144	40	27.8	119	25	21.0	247			269		
	life limiting neurodisability	183	37	20.2	22			33	10	30.3	61	17	27.9	67		
12 to 17	all	2187	165	7.5	388	60	15.5	364	45	12.4	1019	45	4.4	416	15	3.6
	no comorbidity	666	17	2.6	97	6	6.2	83			376	7	1.9	110		
	any comorbidity	1521	148	9.7	291	54	18.6	281			643	38	5.9	306		
	one body system	574	28	4.9	97	10	10.3	99			290	9	3.1	88		
	more than one body system	947	120	12.7	194	44	22.7	182			353	29	8.2	218		
	life limiting neurodisability	157	30	19.1	42			29	10	34.5	46			40		

Cells with <5 cases are supressed, as have cells which allow calculation of PICU admissions where there are <5 cells

Figure Captions

Figure 1 Monthly hospitalizations due to Primary COVID-19 and estimated new SARS-CoV-2 infections in under 18 year olds in England.

Figure 2 Adjusted odds ratios of admission to PICU with Primary COVID-19 within CYP with main comorbidity groups
A Any comorbidity
B Number of body systems
C Life limiting neurodisability

Notes: Results of GEE models showing odds ratios of PICU admission adjusted for age, sex, ethnicity and IMD quintile group in selected comorbidity compared with no comorbidity. The red line indicates odds ratio of 1