Risk factors for PICU admission and death amongst children and young people hospitalized with COVID-19 and PIMS-TS in England during the first pandemic year

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Abstract

Identifying which children and young people (CYP) are most vulnerable to serious SARS-CoV-2 infection is important to guide protective interventions.

To address this question we used data for all hospitalizations in England in 0-17 year olds from 1st Feb 2019 - 31st Jan 2021. We examined how sociodemographic factors and comorbidities may be risk factors for Pediatric Intensive Care Unit (PICU) admission within hospitalizations due to: COVID-19 and Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) in the first pandemic year (2020-21), all other non-traumatic causes in 2020-21, all non-traumatic causes in 2019-20, and hospitalizations due to influenza in 2019-20.

Risk of PICU admission and death from COVID-19 or PIMS-TS amongst CYP was very low. We identified 6,338 COVID-19 hospitalizations, of which 259 were admitted to PICU and 8 died, and 712 PIMS-TS hospitalizations, of which 312 were admitted to PICU and < 5 died. Hospitalizations with COVID-19 and PIMS-TS were more common amongst males, older CYP, those from socio-economically deprived neighbourhoods, and those who were non-White ethnicity (Black, Asian, mixed or other).

Odds of PICU admission were: increased amongst CYP aged under 1 month and decreased amongst 15-17 year olds compared with 1-4 year olds with COVID-19; increased in older CYP and females with PIMS-TS, increased for Black compared with White ethnicity in COVID-19 and PIMS-TS patients. Odds of PICU admission in COVID-19 were increased for CYP with comorbidities, and highest for CYP with multiple medical problems. Increases in odds of PICU admission associated with different comorbidities in COVID-19 showed a similar pattern to other causes of hospitalization examined, and so likely reflect background vulnerabilities. These findings identify distinct risk factors associated with PICU admission among CYP with COVID-19 or PIMS-TS that may aid treatment and prevention strategies.

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Main Text

Introduction

Most children and young people (CYP) experience a mild disease following SARS-CoV-2 infection compared with adults,[1-3] and asymptomatic infection is common.[4] However, severe clinical outcomes have been reported amongst CYP due to COVID-19 and to Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C), including a small number of deaths.[2,5-9] Understanding which CYP are vulnerable to increased risk is important to guide clinicians, families and policymakers in relation to protective shielding and potential vaccination strategies.

Early in the pandemic, guidance from the UK Royal College of Paediatrics and Child Health (RCPCH) identified CYP with immunodeficiency or immunosuppression, and those with certain malignancies, as having the greatest vulnerability to COVID-19.[10] However, CYP with a broad range of other conditions have also been highlighted as being potentially clinically extremely vulnerable (CEV). CYP who are identified as CEV have been advised to take additional "shielding" precautions to reduce the risk of SARS-CoV-2 infection in many countries. These include measures that may result in harm to CYP and their families, including those associated with reduced social mixing and restriction of in-person schooling.

Clear guidance is urgently needed on which CYP are at higher risk of poorer outcomes of SARS-CoV-2 infection in order to limit harms due to inappropriate shielding. The rarity of severe and fatal COVID-19 in CYP means that large-scale population-based studies are needed to identify CYP at greatest risk. Theses analyses also need to take into account background risks for severe illness that preceded the pandemic; CYP who are at increased risk of severe disease due to SARS-CoV-2 infection may also be those who are vulnerable to other respiratory viruses such as influenza.[11]

We used national linked administrative health data (Secondary Use Services data (SUS), linked with the national SARS-CoV-2 database, pediatric intensive care data, and national mortality data) to analyse all hospital admissions due to COVID-19 or PIMS-TS amongst CYP

in England from Feb 2020 – Jan 2021. Among these admissions, we examined how sociodemographic factors and pre-existing conditions recorded over the previous 5 years (from 2015/16 to 2020/21) were associated with odds of admission to a Pediatric Intensive Care Unit (PICU), which we used as a proxy for serious disease, or death. To understand if these risk factors were specific to SARS-CoV-2, represented background vulnerabilities or reflected changes to healthcare activity caused by the pandemic, we then repeated this analysis amongst CYP admitted with other causes of admission that year, and admissions during 2019-20 including those due to influenza.

Results

There were 1,242,197 emergency non-traumatic hospital admissions in England (hereafter "admissions") between 01 Feb 2019 and 31 Jan 2021 involving 892,906 CYP; 699,397 (78%) had only one admission. During 2020-21, there were 470,606 admissions: 6,338 with COVID-19 amongst 5,830 CYP; 712 with PIMS-TS amongst 690 CYP and 463,556 for other causes amongst 367,637 CYP. In comparison, there were 771,591 admissions for 587,115 CYP during 2019-20, of which 6968 were due to influenza in 6,780 CYP (see supplementary material 1 table S1 and S15). 69.8% of CYP admitted due to PIMS-TS had no prior hospital admissions, compared with 49.5-54.4% in all other cohorts.

The distribution of admissions by age, sex and ethnicity differed between the COVID-19, PIMS-TS, and other cohorts (Table 1). A higher proportion of the PIMS-TS cohort was male (63.5%) compared to the other cohorts (52.8-54%). Overall, 30.9% of admissions with COVID-19 were in infants (children aged under 1 year, including neonates under 1 month of age, and post neonatal infants aged 1-11 months), similar to other pandemic year admissions and total admissions in 2019-20, but more than for influenza (17.1%) during this time period. Amongst PIMS-TS, only 10.3% of admissions were in infants, whereas >85% were among 1-14 year-olds. CYP with non-White ethnicity made up 41.9% of COVID-19 admissions, and 60.0% of PIMS-TS admissions, higher than the other hospitalization cohorts we examined. There were more admissions in CYP from more deprived neighbourhoods compared with least deprived in all cohorts, as assessed using Index of Multiple Deprivation (IMD) quintile category. Further description of how IMD is determined is available in the supplementary material.

Amongst COVID-19 admissions, 53.9% had a recorded comorbidity, and 18.0% had a life limiting comorbidity, higher than for other pandemic year admissions, all admissions in 2019-20, and influenza admissions in 2019-20 (Supplementary Table S1). Patterns of comorbidities amongst admissions with PIMS-TS were different to the other cohorts, with 68.3% having any comorbidity recorded, of which 20.6% were life-limiting. Due to the multi-system nature of PIMS-TS, and of limitations in how data are recorded within SUS, many of the comorbidities recorded could have been related to complications of the disease, rather than prior conditions. Although 40.2% of PIMS-TS admissions had a cardiovascular

138 comorbidity recorded, only 5.3% had a congenital cardiac condition, with remaining codes
139 including arrhythmias and aneurysms, which may reflect the disease process. When non-
140 congenital cardiac conditions, blood disorders and anemias were excluded, only 15.9% of
141 PIMS-TS admissions had a comorbidity recorded, compared with 30-35% in the other
142 cohorts.
143
144 *Outcomes following admission*
145 Table 2 shows total numbers and proportions of PICU admissions within each cohort by
146 comorbidity category, with additional data for all comorbidities examined in Supplementary
147 material 1 Tables S3-S5. Across COVID-19 admissions, 259 (4.1%) were admitted to PICU,
148 compared with 312 (43.8%) of PIMS-TS admissions, 5016 (1.1%) of other pandemic year
149 admissions, 7282 (0.9%) of all admissions in 2019-20 and 161 (2.3%) of influenza admissions
150 in 2019-20.
151
152 Twenty nine CYP admitted with COVID-19 died within 28 days of hospitalisation. Of these, 8
153 were confirmed as likely caused by SARS-CoV-2 infection after reviewing case notes and
154 death notification data. All had a comorbidity recorded and 7/8 had a life-limiting condition.
155 Six CYP died within 28 days of an admission with PIMS-TS, of which < 5 were thought to be
156 caused by the disease.
157
158 *Sociodemographic factors*
159 In multivariable models adjusting for all factors and the presence of comorbidities, female
160 sex was associated with increased odds of PICU admission for PIMS-TS, and reduced odds
161 amongst all admissions 2019-20, with no associations found by sex for COVID-19 or the
162 other cohorts (supplementary material 1, tables S11-S15). Compared with admissions
163 amongst 1-4 year olds, odds of PICU admission for COVID-19 were increased amongst
164 neonates (CYP aged less than 1 month) and decreased amongst 15-17 year olds, similar to
165 patterns for other pandemic year admissions and all admissions 2019-20, (although odds
166 were also decreased for 5-14 year olds in these cohorts). Odds of PICU admission for PIMS-
167 TS increased with age in a stepwise fashion and were highest in 15-17 year olds. The odds of
168 PICU admission within influenza admissions in 2019-20 were only higher amongst neonates
169 compared with 1-4 year olds.

Compared with White CYP, odds of PICU admission were higher amongst Black CYP for COVID-19 and Black, Asian and CYP with unknown ethnicity for PIMS-TS. Other pandemic year admissions and all admissions 2019-20 showed a pattern of higher odds of PICU admission in non-White ethnic groups, with no evident differences by ethnicity amongst influenza admissions in 2019-20. There were no significant differences in odds of PICU admission by IMD category for COVID-19, all admissions in 2019-20 and influenza admissions in 2019-20. In contrast, odds of PICU admission were increased in less deprived categories amongst PIMS-TS admissions, and amongst other pandemic year admissions.

Comorbidities

The odds of admission to PICU were increased amongst CYP with any comorbidity compared with no comorbidity in all cohorts (supplementary material 2). The increases in odds of PICU admission associated with having each of any comorbidity, a life-limiting comorbidity, or comorbidities in more than one body system for COVID-19 (Figure 1), had overlapping confidence intervals with those for all admissions in 2019-20 and influenza admissions in 2019-20, but were lower than for other pandemic year admissions. Odds ratios for PIMS-TS admissions were consistently the lowest of any cohort for each comorbidity category, although confidence intervals often overlapped.

For body system comorbidities (Figure 2), odds ratios for the increase associated with cancer/haematological conditions, neurological, respiratory, neurological with respiratory and respiratory with cardiovascular comorbidities in COVID-19 appeared comparable to influenza and all admissions in 2019-20 but not PIMS-TS (where the increase in odds was lower) or other pandemic year admissions (where the increase in odds was higher). The increase in odds for cardiovascular comorbidities within COVID-19 appeared similar to that seen in all admissions in 2019-20, but higher than influenza admissions 2019-20 and PIMS-TS, and lower than for other pandemic year admissions. A similar pattern was observed for combinations of body-system comorbidities (Figure 3), i.e. that the increase in odds for COVID-19 appeared similar to that for influenza and all admissions 2019-20, but was higher than for PIMS-TS and lower than in other pandemic year admissions.

Asthma, diabetes, epilepsy and trisomy 21 each increased risk of PICU admission for COVID-19, although sickle cell disease did not (Figure 4). Increases in odds for COVID-19 appeared broadly similar to those for other cohorts although confidence intervals were wide, particularly for PIMS-TS.

Results from sensitivity analyses where data were restricted to 11-17 year olds to guide vaccination policy are shown in supplementary material 1 figures S1-S4 and supplementary material 3. Patterns of odds ratios were similar, although female sex was associated with significantly reduced odds of PICU admission for COVID-19. Increases in odds of PICU admission associated with comorbidities for COVID-19 amongst 11-17 year olds were lower than when all CYP were included for some outcomes. However, due to low numbers, confidence intervals around these estimates were wide. We were not able to model associations within Influenza admissions in 11-17 year olds due to low numbers.

Discussion

We found that very few CYP admitted to hospital in England due to COVID-19 or PIMS-TS went on to develop severe disease or die. Of the 12.02 million 0-17 year olds in England during 2020, 1 in 2062 (n= 5830) were admitted to hospital due to COVID-19, and 1 in 47,903 (n=251) were admitted to PICU. This represented only 1.3% of all secondary care admissions in the pandemic year and less than 5% of non-traumatic emergency PICU admissions. Eight of these CYP died within 28 days of admission to hospital. For PIMS-TS, 1 in 17,425 (n=690) of CYP in England were admitted to hospital, 1 in 38,911 (n=309) were admitted to PICU, and fewer than 5 children died. This likely represents all PIMS-TS cases nationally over the study period, as the vast majority will have required hospitalisation.

CYP admitted to hospital with COVID-19 and PIMS-TS were older and more likely to be non-white than in the other cohorts examined. For COVID-19, we found the odds of PICU admission increased amongst neonates compared with 1-4 year-olds, and those who were Black compared with White ethnicity, but found no associations by deprivation. Female sex was associated with significantly lower olds of PICU admission for COVID-19, but only in sensitivity analyses where data were restricted to 11-17 year olds. For PIMS-TS, the odds of PICU admission were increased amongst females, older CYP and those from non-White ethnic groups.

Of the 251 CYP admitted to PICU with COVID-19, 91% (n=229) had an underlying condition or comorbidity. The odds of PICU admission due to COVID-19 were increased in all comorbidity categories tested except sickle cell disease. We found that CYP with complex medical problems across multiple body systems, and those with neurodisability, were at greatest risk. This pattern is described in previous work,[12] and is consistent with our meta-analysis of the published data, where each increase in number of pre-existing conditions was associated with increased odds of PICU admission and death for COVID-19 [R. Hardwood et. Al, unpublished[13]]. Increases in odds of PICU admission associated with comorbidities in PIMS-TS were lower than for COVID-19, but are difficult to interpret; coding of PIMS-TS admissions suggested two-thirds had a comorbidity, whilst three quarters had no prior admissions to hospital. When codes which include known cardiac and haematological complications of PIMS-TS were excluded, estimates for comorbidities in these admissions

dropped to around 15%, similar to work from the UK and US showing the majority of CYP admitted with PIMS-TS or MIS-C were previously healthy.[8,14]

Our comparison with other causes of admission allowed us to assess whether these risk factors are specific to COVID-19 or PIMS-TS, or reflect background vulnerability to serious illness. Our findings that non-White ethnic groups (ie CYP who were of Asian and Black ethnicity) was associated with increased odds of serious disease was similar to findings from other cohorts except for influenza. However, a high proportion of admissions for COVID-19 and PIMS-TS were from non-White ethnic groups, consistent with previous work,[15-17] and increases in odds associated with non-White ethnicity were greater in these cohorts, similar to findings in adults.[18,19] Age-patterns for COVID-19, and particularly for PIMS-TS admission, were notably shifted towards older age-groups in comparison with other cohorts, including influenza. We only found significant sex differences in risk for COVID-19 amongst 11-17 year olds, unlike other pandemic-year admissions and all admissions in 2019-20, where female sex was associated with lower odds of PICU admission in all models. Almost two thirds of PIMS-TS admissions were amongst males, higher than in all other cohorts, but odds of PICU admission were greater amongst females.

We found broadly similar increases in odds for PICU admission associated with number of body systems or type of comorbidities across COVID-19, all 2019-20 admissions and influenza admissions. Increases in odds were highest for combinations of body system comorbidities e.g. neurological and respiratory, neurological and cardiovascular and respiratory and cardiovascular. Similarly, for the specific conditions examined, odds ratios overlapped with those for other pandemic year, all admissions 2019-20 and influenza, with the exception of sickle cell disease which was not associated with an increased odds of PICU admission for COVID-19 or influenza.

When absolute risk was examined, the increases in risk associated with comorbidities were relatively small in the COVID-19, other pandemic year, all admissions 2019-20 and influenza cohorts, although greater for COVID-19 than other groups. For example, for the 229 CYP with comorbidity in one body system admitted to PICU with COVID-19, the increase in risk above those without comorbidities was 2% for COVID-19, 0.75% for all admissions in 2019-20 and 1.3% for influenza. Combinations of comorbidities increased risk the most, although

again numbers were very small. Amongst the 414 admissions with respiratory and neurological comorbidities, the increase in risks were 18.6% for COVID-19 compared with 12.3% for influenza and 7-8% for other cohorts. Whilst this greater increase in absolute risk with COVID-19 appeared significant for body system comorbidities and their combinations, confidence intervals overlapped for all specific conditions.

Our finding that the pattern of risks for severe COVID-19 related to comorbidities is similar to that for other reasons for admission suggests these reflect underlying vulnerabilities to illness and infection. A similar observation has been made in adults when risks were examined across COVID-19 and non-COVID deaths during the pandemic.[20] However, whilst the pattern of risks was very similar and absolute risks remained relatively small, increases in absolute risk of PICU admission were often higher for COVID-19 than for other cohorts including influenza. This suggests that SARS-CoV-2 infection may magnify underlying risks faced by CYP with chronic and life-threatening conditions. It is also possible that these findings reflect changes in health system factors during the pandemic, although other studies have suggested there was no overall change in thresholds for PICU admission in England.[21]

Patterns within admissions due to COVID-19 amongst CYP, (older age, non-White ethnicity and presence of comorbidities), are very similar to those identified for adults.[18,19] This suggests that the strong age-related risk of severe disease in adult COVID-19[19,22] extends across the early life-course, but has previously been difficult to uncover in CYP due to the extreme rarity of severe disease.

Strengths and Limitations

Previous work examining risk factors for severe disease and death from SARS-CoV-2 in CYP have predominantly used dedicated reporting systems, and analysed data in the first months of the pandemic.[8,9,15,16] In contrast, our study utilises unique population level data from a large country with a high burden of disease due to COVID-19, and includes all CYP admissions over the first pandemic year. We also uniquely examine data from previous years to provide context to our risk estimates. Our study is subject to a number of limitations. We are unable to account for the effect of protective shielding on differential exposure to SARS-Cov-2 among CYP thought to be vulnerable, which may have affected our

estimates. However, our findings relate to risk factors for severe disease once hospitalised, whereas shielding is likely to bias estimates of risk factors for infection, which we did not examine.

As the pandemic progresses and variants continue to emerge, the risks posed by SARS-CoV-2 amongst CYP may change. Our data included children infected with the Alpha variant (from November 2020 onwards) but did not include children infected with the Delta (B.1.617.2) variant, dominant in the UK since May 2021. The Delta variant has higher transmissibility, and prevalence, and there have been suggestions of greater severity in CYP, although the evidence for this is mixed.[23] Further population-level analyses are needed to explore the effect of this and other factors on disease severity in CYP as new data become available.

Although use of Secondary Uses Service (SUS) data allowed us to examine the burden of severe disease associated with SARS-CoV-2 and risk factors in CYP at population level, there are a number of limitations to SUS data. Missing or inaccurate data fields within SUS or other datasets, and incomplete data linkage, may have affected our findings. We included both cause of admission and PCR testing for SARS-Cov-2 to identify CYP with COVID-19 to ensure we capture all likely cases, but this will have affected our case definition specificity. Identifying PIMS-TS cases was particularly problematic, as ICD-10 codes for this condition were only introduced several months into the pandemic. We included CYP coded with Kawasaki disease and systemic inflammatory response syndrome when examining PIMS-TS, some of whom will not have had PIMS-TS (note that not all PIMS-TS cases had evidence of previous SARS-CoV-2 infection by PCR). Coding for PIMS-TS is likely to improve as knowledge of the condition increases, which will benefit future analyses of PIMS-TS admissions using hospital administrative data. There is also variation in case definition used for diagnosing post inflammatory syndromes related to SARS-CoV-2 (e.g. MIS-C and PIMS-TS), which may affect the generalizability of our results. However, in practice the vast majority of CYP will have fulfilled both criteria.[8,15]

We were unable to fully distinguish between admissions *with* COVID-19 and those *due to* COVID-19, and some of the admissions we classify as COVID-19 will include those with

incidental positive PCR tests. We used admission to PICU as an indicator for disease severity and were not able to examine the level of intensive support needed whilst in critical care. Our results may also have been affected by changes to thresholds for PICU admission, and coding practices, as the pandemic progressed and in comparison to the previous years. Our estimate for number of deaths due to COVID-19 and PIMS-TS only include hospitalised CYP, and so will not include those who died at home or in an emergency department prior to admission. Note that our linked study of all CYP deaths up to 28th Feb 2021 identified 25 deaths across all places of death, and provides a more complete analysis of mortality risk associated with SARS-CoV-2.[24]

We use ICD-10 codes developed to identify chronic conditions across five years of admission data, and may have missed diagnoses recorded prior to this. We were not able to account for the wide range of disease severity included within the diagnostic groups used for coding purposes in our analysis. Further, the ICD-10 codes we used included some diagnoses which may relate to complications of acute disease, rather than pre-existing conditions only, as highlighted with PIMS-TS. We were unable to only include comorbidities prior to the index case to investigate this further as many CYP had no prior records, and this approach would not account for incomplete coding in previous admissions or diagnoses made in primary care. Linking SUS data with national primary care records would improve identification of pre-existing conditions for these analyses, but these data are currently not available. Our analysis of individual or body system comorbidities does not account for CYP with both the comorbidity of interest and other conditions. However, we do assess odds of PICU by number of body systems involved, which does address identifying CYP with multiple medical problems. Finally, due to incomplete coding we were unable to examine some important risk factors for severe disease in adults in these analyses, including obesity,[25] which should be the focus of future study.

In conclusion, in marked contrast to adults, CYP were at very low risk of severe disease and death from COVID-19 or PIMS-TS during the first pandemic year. In the rare instances when CYP did require hospitalisation, risk factors for severe disease were similar to those reported for adults. Additionally, the pattern of comorbidities was similar to that seen with influenza and all admissions in 2019-20, reflecting underlying vulnerabilities to infection, although COVID-19 magnified these risks to a small degree. We identified important demographic

factors which were associated with PICU admission due to PIMS-TS, although associations between comorbidities and PICU admission in this group were difficult to interpret.

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Author contribution statement

Study design was developed by all authors. Data cleaning and analysis was undertaken by JLW, LKF and RMV. Data interpretation was undertaken by all authors. The first draft was written by JLW. All authors contributed to editing and reviewing the final manuscript.

Competing Interest Statement

The authors declare there are no competing interests

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Tables

Table 1 Number and proportion of admissions by sociodemographic characteristics within each cohort (COVID-19, PIMS-TS, other pandemic year admissions; all admissions in 2019-20; influenza admissions in 2019/20)

		2020/21						2019/20			
		COVID-19		PIMS TS		Other pandemic year admission		All admissions 2019/20		Influenza 2019/20	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total		6338	(100.0)	712	(100.0)	463556	(100.0)	771591	(100.0)	6968	(100.0)
Sex	Male	3347	(52.8)	452	(63.5)	247299	(53.3)	416830	(54.0)	3733	(53.6)
	Female	2991	(47.2)	260	(36.5)	216257	(46.7)	354761	(46.0)	3235	(46.4)
Age	Neonates	741	(11.7)	<5	.	69230	(14.9)	89822	(11.6)	151	(2.2)
	Post neonatal	1216	(19.2)	71	(10.0)	71560	(15.4)	135195	(17.5)	1036	(14.9)
	1 to 4	1281	(20.2)	217	(30.5)	126426	(27.3)	262511	(34.0)	3189	(45.8)
	5 to 9	840	(13.3)	216	(30.3)	71255	(15.4)	116951	(15.2)	1274	(18.3)
	10 to 14	1188	(18.7)	175	(24.6)	72256	(15.6)	97662	(12.7)	871	(12.5)
	15 to 17	1072	(16.9)	31	(4.4)	52829	(11.4)	69450	(9.0)	447	(6.4)
Ethnicity	White	3685	(58.1)	285	(40.0)	329358	(71.1)	544460	(70.6)	4653	(66.8)
	Mixed	279	(4.4)	51	(7.2)	20426	(4.4)	33397	(4.3)	259	(3.7)
	Asian	1203	(19.0)	155	(21.8)	49217	(10.6)	88615	(11.5)	1063	(15.3)
	Black	395	(6.2)	109	(15.3)	17388	(3.8)	30948	(4.0)	333	(4.8)
	Other	298	(4.7)	40	(5.6)	13160	(2.8)	22381	(2.9)	197	(2.8)
	Unknown	478	(7.5)	72	(10.1)	34007	(7.3)	51790	(6.7)	463	(6.6)
IMD Quintile Category	Most deprived	1662	(26.2)	163	(22.9)	108096	(23.3)	188391	(24.4)	1906	(27.4)
	2nd most deprived	1533	(24.2)	182	(25.6)	96386	(20.8)	163405	(21.2)	1497	(21.5)
	3rd most deprived	1218	(19.2)	164	(23.0)	92034	(19.9)	152297	(19.7)	1278	(18.3)
	4th most deprived	1087	(17.2)	98	(13.8)	87873	(19.0)	142097	(18.4)	1197	(17.2)
	Least deprived	838	(13.2)	105	(14.7)	78982	(17.0)	125167	(16.2)	1090	(15.6)
	Missing	0	(0.0)	0	(0.0)	185	(0.0)	234	(0.0)	0	(0.0)

Table 2 Total admissions and proportion resulting in pediatric critical care admission (PICU) by selected comorbidity groups within each cohort (COVID-19, PIMS-TS, other pandemic year admissions; all admissions in 2019/20; influenza admissions in 2019/20)

		COVID 19			PIMS TS			Other pandemic year admission			All admissions 2019/20			Influenza 2019/20		
		n	PICU	% PICU	n	PICU	% PICU	n	PICU	% PICU	n	PICU	% PICU	n	PICU	% PICU
	Total	6338	259	(4.1)	712	312	(43.8)	463556	5016	(1.1)	771591	7282	(0.9)	6968	161	(2.3)
Any comorbidity	No comorbidity	2923	22	(0.8)	258	50	(19.4)	242245	358	(0.1)	417842	811	(0.2)	3859	30	(0.8)
	Comorbidity present	3415	237	(6.9)	454	262	(57.7)	221311	4658	(2.1)	353749	6472	(1.8)	3109	131	(4.2)
Number of body systems	1 body system	1396	35	(2.5)	182	76	(41.8)	114597	1015	(0.9)	185453	1436	(0.8)	1449	29	(2.0)
	More than 1 body system	2019	202	(10.0)	272	186	(68.4)	106714	3643	(3.4)	168296	5036	(3.0)	1660	102	(6.1)
Life limiting or non-life limiting comorbidity	Non-life-limiting comorbidity	2272	79	(3.5)	307	157	(51.1)	169415	1701	(1.0)	272959	2323	(0.9)	2065	43	(2.1)
	Life-limiting comorbidity	1143	158	(13.8)	147	105	(71.4)	51896	2957	(5.7)	80790	4149	(5.1)	1044	88	(8.4)

Figure captions

Figure 1 Odds ratios and percentage point difference in predicted probability with 95% confidence intervals for admission to PICU by comorbidity groups within each cohort, adjusted for age, sex, IMD category, ethnicity

Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the right panel. Observations: n=6338 COVID-19 admissions; n=710 PIMS-TS admissions; n= 463371 other pandemic year admissions; n=771357 all admissions 2019-20; n=influenza admissions 2019-20. These results are available in full in supplementary material part 2.

Figure 2 Odds ratios and percentage point difference in predicted probability with 95% confidence intervals for admission to PICU by body system comorbidities within each cohort, adjusted for age, sex, IMD category, ethnicity

Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the middle panel. Number of observations in each model is shown in the right panel. These results are available in full in supplementary material part 2.

Figure 3 Odds ratios and predicted probability with 95% confidence intervals for admission to PICU by comorbidity combinations within each cohort, adjusted for age, sex, IMD category, ethnicity

Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the middle panel. Number of observations in each model is shown in the right panel. These results are available in full in supplementary material part 2.

Figure 4 Odds ratios and predicted probability with 95% confidence intervals for admission to PICU by selected diagnoses within each cohort, adjusted for age, sex, IMD category, ethnicity

Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD

category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the middle panel. Number of observations in each model is shown in the right panel. These results are available in full in supplementary material part 2.

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Methods

Data

We used Secondary Use Services (SUS), an administrative national database covering ~98% of National Health Service (NHS) hospital activity in England.[26] Data were available for admissions due to any cause in CYP aged 0-17 years in England between March 1st 2015 to Feb 28th 2021 (n=11,467,027). Note this does not include accident and emergency attendances not resulting in hospital admission. Coded fields included reason for hospital admission, co-morbidities, and sociodemographic characteristics. We primarily examined admissions occurring from 1st Feb 2019 – 31st Jan 2021, but to account for variable quality and completeness of coding within SUS, we used all available data (2015-2021) from all types of admission (emergency, elective and maternal) to populate socio-demographic and comorbidity data for CYP.

As clinical details are limited in SUS, and to aid identification of COVID-19 and PIMS-TS admissions, these data were deterministically linked using unique patient NHS numbers to the following healthcare datasets:

1) Paediatric Intensive Care Audit Network (PICANet) data containing all Paediatric Intensive Care (PICU) admissions in England.
2) Death registrations provided by the Office for National Statistics (ONS).
3) National Child Mortality Database (NCMD), which collects preliminary notification data within 48 hours of death of a CYP death in England and Wales
4) SARS-CoV-2 PCR-testing data provided by Public Health England (PHE).

Outcomes and Exposures

We examined associations between severity outcomes (PICU admission or death) and the following exposures: reason for hospital admission (COVID-19, PIMS-TS, other), sociodemographic factors and presence of comorbidities.

We linked hospitalisations in SUS to PICANet data if the PICU admission date occurred during or within one day of the SUS admission or discharge date, to account for coding error in either dataset. We defined admissions resulting in death as the last admission for each

CYP that occured within 28 days of death identified through ONS or NCMD. All NCMD deaths during the pandemic were clinically reviewed as part of a separate analysis [Smith, C et al 2021 (currently under peer review)] to identify the contribution of SARS-CoV-2 infection and PIMS-TS to death.

Reason for admission

We used primary and secondary diagnoses coded to International Classification of Diseases 10 (ICD 10) to define all hospital admissions between 1st Feb 2019 and 31st Jan 2021. We excluded all traumatic admissions (where the primary cause of admission was an external cause in ICD-10), and non-emergency admissions (i.e. elective or maternity/newborn) from the analysis, and classified the remainder into five cohorts:

- admissions due to COVID-19 (1st Feb 2020 – 31st Jan 2021);
- admissions due to PIMS-TS (1st Feb 2020 – 31st Jan 2021);
- all other admissions during the pandemic year (1st Feb 2020 – 31st Jan 2021);
- all admissions in the year prior to the pandemic (1st Feb 2019 – 31st Jan 2020);
- all admissions where the primary diagnosis was influenza in the year prior to the pandemic (1st Feb 2019 – 31st Jan 2020).

We defined COVID-19 admissions as those occurring after Feb 1st 2020 with relevant ICD-10 codes recorded as reason for admission, or (using linked data) where there was a positive PCR test for SARS-CoV-2 within 7 days of admission or discharge, (unless this occurred at least 7 days after admission to PICU, and nosocomial infection was likely).

We defined PIMS-TS admissions those occurring after 1st Feb 2020 with ICD-10 codes recorded as reason for admission for either PIMS-TS (introduced November 2020), or Kawasaki disease or systemic inflammatory response syndrome, (used as proxies for PIMS-TS prior to November 2020).

To improve the identification of COVID-19 and PIMS-TS, we also reviewed details of all PICU admissions during the first pandemic year held within PICANet. Where treating specialists determined the PICU admission was due to either COVID-19 or PIMS-TS, we recoded the

SUS admission accordingly. Hospital admissions identified as both due to COVID-19 and PIMS-TS were defined as being due to PIMS-TS, as we assumed the COVID-19 diagnosis was part of the same disease process.

Socio-demographic exposures

Age was categorised as neonates (admission within 1 month of birth), post-natal infants (admission between 1 – 11 months of birth), 1-4 years, 5-9 years, 10-14 years and 15-17 years. We defined 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 of CYP. Further details of how IMD is defined are available in supplementary material 1.

Co-morbidities

We used published literature and guidance on shielding to identify co-morbidities likely to increase risk of severe SARS-CoV-2 disease.[10,13] We identified CYP with chronic medical conditions by body system, those with life-limiting conditions, and those with asthma, diabetes, epilepsy, sickle cell disease and trisomy 21, using recognised ICD-10 code lists.[27,28] Note that admissions amongst CYP with specific conditions were also included in the broader body system diagnostic categories. We then defined additional co-morbidity groups to examine vulnerability associated with multiple medical problems. These were defined as: comorbidities in more than one body system; comorbidities in both neurological and respiratory, neurological and cardiovascular, or respiratory and cardiovascular body systems. We compared admissions amongst CYP with each comorbidity category to CYP with no comorbidities in any category in all analyses.

Statistics and Reproducibility

First we described the characteristics of each of the five cohorts: admissions due to COVID-19, admissions due to PIMS-TS, other non-traumatic admissions in 2020/21 (hereafter "other pandemic year admissions"), all non-traumatic admissions in 2019/20, and admissions due to influenza in 2019/20. We supressed cell counts with small numbers (where n < 5) due to the risk of identification of individuals, in line with guidance from data providers used in this study.

We then modelled the association between sociodemographic factors and co-morbidities with PICU admission within each cohort separately. Sample sizes for these analyses were determined by the number of admissions identified within the SUS data, after non-emergency admissions, or those due to trauma, were excluded. Investigators were not blinded, and experiments were not randomized. All analyses were performed in Stata 16 (StataCorp, College Station TX). Models employed generalized estimation equations (GEE) using the *xtgee* command in order to account for multiple admissions within the same CYP across and within different cohorts. Models used a logit link, specifying the covariance structure as "exchangeable" (i.e. we assumed equal correlations between any two admissions within one CYP). We then calculated the difference in predicted probability for PICU admission amongst those with and without each comorbidity category using the *margins* post estimation command. We used univariable and then multivariable models to estimate the odds of PICU admission within each cohort by the presence of specific comorbidities compared with CYP with no comorbidities across any diagnostic category (dichotomous or ordinal variable), adjusted for: age group (categorized as: infant, 1-4, 5-9, 10-14, 15-17 years), sex, ethnic group (categorized as: White, Mixed, Asian, Black, Other) and IMD category (categorized as lowest – highest quintile category). Comparisons between cohorts were not tested; significance was inferred if 95% confidence intervals did not overlap. We were unable to model death as an outcome in these analyses due to low numbers. In sensitivity analyses, we repeated analyses to only include secondary school age CYP to inform vaccination policy (i.e. ages 11-17).

Ethics approval and legal basis for data linkage and analyses

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).

Informed consent was not obtained to use hospital administrative data for research purposes. Patients have the ability to opt out of their personal/confidential information being shared by NHS Digital and Public Health England, and all other health and care organisations included in this analysis, for purposes not related to their own direct care.

Further information regarding the national opt-out can be found at: https://www.nhs.uk/your-nhs-data-matters/manageyour-choice/ Current Control Of Patient Information (COPI) regulations provide a legal basis for linking datasets used in this study without consent.[29] Low numbers (n <5) are supressed to reduce risk of identification of patients.

NCMD

The NCMD legal basis to collect confidential and personal level data under the Common Law Duty of Confidentiality has been established through the Children Act 2004 Sections M - N, Working Together to Safeguard Children 2018 (https://consult.education.gov.uk/child-protection-safeguarding-and-family-law/working-together-to-safeguard-children-revisions-t/supporting_documents/Working%20Together%20to%20Safeguard%20Children.pdf) and associated Child Death Review Statutory & Operational Guidance https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/859302/child-death-review-statutory-and-operational-guidance-england.pdf). The NCMD legal basis to collect personal data under the General Data Protection Regulation (GDPR) without consent is defined by GDPR Article 6 (e) Public task and 9 (h) Health or social care (with a basis in law).

PICANet

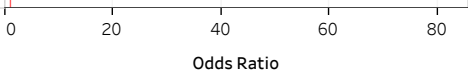
Processing of personally identifiable data for the purposes of service evaluation, audit, and research was approved by the Patient Information Advisory Group (now the Health Research Authority Confidentiality Advisory Group) in 2002 under Section 60 of the Health and Social Care Act (subsequently Section 251 of the National Health Service Act 2006) (reference: PIAG 4-07(c) 2002). Permissions to use these data were amended and approved specifically to collect additional data relating to COVID-19 for confirmed and suspected cases.

Data availability Statement

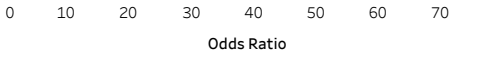
These analyses were undertaken using datasets held by NHS England for the use of ongoing service evaluation, held within the National Commissioning Data Repository. Access to these

676 data at individual level are restricted, as described in data sharing agreements between NHS
677 England and specific data providers, and within the application for ethical approval provided
678 for this study. We were able to access and anlayse these data as employees of NHS England.
679 Researchers wishing to access the individual level data used in this analysis are able to apply
680 to do so via NHS Digital. Aggregated, non-identifiable data used for this study are provided
681 in the supplementary material.
682

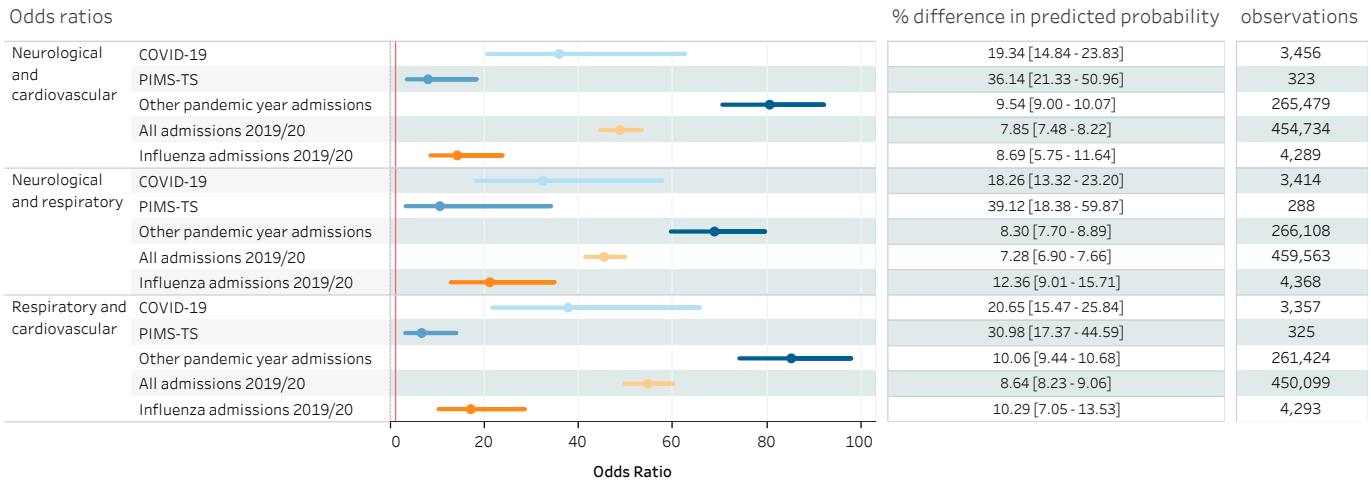
			Odds ratios	% difference in predicted probability
Any comorbidity	Comorbidity present	COVID-19		6.75 [5.64 - 7.86]
		PIMS-TS		28.36 [21.11 - 35.60]
		Other pandemic year admissions		2.55 [2.46 - 2.63]
		All admissions 2019/20		2.01 [1.95 - 2.07]
		Influenza admissions 2019/20		3.62 [2.82 - 4.42]
Life limiting or non life limiting comorbidity	Non life limiting comorbidity	COVID-19		3.02 [2.07 - 3.97]
		PIMS-TS		24.49 [16.69 - 32.28]
		Other pandemic year admissions		1.20 [1.13 - 1.27]
		All admissions 2019/20		0.88 [0.83 - 0.93]
		Influenza admissions 2019/20		1.41 [0.71 - 2.11]
	Life limiting comorbidity	COVID-19		14.36 [11.92 - 16.80]
		PIMS-TS		37.54 [27.70 - 47.38]
		Other pandemic year admissions		7.34 [7.05 - 7.63]
		All admissions 2019/20		6.28 [6.07 - 6.49]
		Influenza admissions 2019/20		8.14 [6.29 - 9.98]
Number of body systems	1 body system	COVID-19		2.03 [1.06 - 3.00]
		PIMS-TS		17.39 [8.72 - 26.06]
		Other pandemic year admissions		0.99 [0.92 - 1.06]
		All admissions 2019/20		0.75 [0.70 - 0.80]
		Influenza admissions 2019/20		1.33 [0.54 - 2.13]
	More than 1 body system	COVID-19		10.91 [9.06 - 12.76]
		PIMS-TS		36.90 [28.68 - 45.11]
		Other pandemic year admissions		4.99 [4.80 - 5.18]
		All admissions 2019/20		3.97 [3.84 - 4.09]
		Influenza admissions 2019/20		5.70 [4.42 - 6.98]



		Odds ratios	% difference in predicted probability	observations
Cancer/ Haematological comorbidity	COVID-19		9.70 [6.90 - 12.50]	3,930
	PIMS-TS		37.84 [28.19 - 47.49]	441
	Other pandemic year admissions		5.30 [4.90 - 5.69]	286,006
	All admissions 2019/20		4.49 [4.24 - 4.75]	484,299
	Influenza admissions 2019/20		4.96 [3.04 - 6.88]	4,654
Cardiovascular comorbidity	COVID-19		15.43 [12.64 - 18.22]	3,961
	PIMS-TS		33.42 [25.50 - 41.34]	542
	Other pandemic year admissions		7.77 [7.46 - 8.08]	289,180
	All admissions 2019/20		6.31 [6.09 - 6.54]	489,665
	Influenza admissions 2019/20		6.29 [4.43 - 8.14]	4,690
Neurological comorbidity	COVID-19		12.31 [9.78 - 14.84]	4,171
	PIMS-TS		27.47 [15.74 - 39.21]	351
	Other pandemic year admissions		4.76 [4.54 - 4.99]	315,855
	All admissions 2019/20		3.75 [3.61 - 3.90]	533,799
	Influenza admissions 2019/20		7.48 [5.70 - 9.25]	4,955
Respiratory comorbidity	COVID-19		11.16 [8.34 - 13.98]	4,101
	PIMS-TS		26.39 [14.48 - 38.29]	361
	Other pandemic year admissions		4.88 [4.61 - 5.16]	312,844
	All admissions 2019/20		3.93 [3.76 - 4.11]	548,982
	Influenza admissions 2019/20		7.61 [5.82 - 9.40]	5,187



Odds Ratio


Odds ratios
% difference in predicted probability
observations
Neurological and cardiovascular
COVID-19
19.34 [14.84 - 23.83]
3,456
PIMS-TS
36.14 [21.33 - 50.96]
323
Other pandemic year admissions
9.54 [9.00 - 10.07]
265,479
All admissions 2019/20
7.85 [7.48 - 8.22]
454,734
Influenza admissions 2019/20
8.69 [5.75 - 11.64]
4,289
Neurological and respiratory
COVID-19
18.26 [13.32 - 23.20]
3,414
PIMS-TS
39.12 [18.38 - 59.87]
288
Other pandemic year admissions
8.30 [7.70 - 8.89]
266,108
All admissions 2019/20
7.28 [6.90 - 7.66]
459,563
Influenza admissions 2019/20
12.36 [9.01 - 15.71]
4,368
Respiratory and cardiovascular
COVID-19
20.65 [15.47 - 25.84]
3,357
PIMS-TS
30.98 [17.37 - 44.59]
325
Other pandemic year admissions
10.06 [9.44 - 10.68]
261,424
All admissions 2019/20
8.64 [8.23 - 9.06]
450,099
Influenza admissions 2019/20
10.29 [7.05 - 13.53]
4,293
0
20
40
60
80
100
Odds Ratio

		Odds ratios	% difference in predicted probability	observations
Asthma	COVID-19		4.50 [1.67 - 7.33]	3,541
	PIMS-TS		9.32 [-2.54 - 21.18]	305
	Other pandemic year admissions		1.37 [1.12 - 1.63]	282,815
	All admissions 2019/20		1.19 [1.03 - 1.35]	494,995
	Influenza admissions 2019/20		2.26 [0.40 - 4.12]	4,540
Diabetes Mellitus	COVID-19		10.96 [2.69 - 19.22]	2,951
	PIMS-TS		42.56 [-9.24 - 94.35]	260
	Other pandemic year admissions		5.84 [4.68 - 7.00]	250,458
	All admissions 2019/20		3.94 [3.16 - 4.72]	428,571
	Influenza admissions 2019/20		2.44 [-3.61 - 8.50]	3,718
Epilepsy	COVID-19		13.67 [8.77 - 18.58]	3,316
	PIMS-TS		50.43 [20.37 - 80.50]	270
	Other pandemic year admissions		6.48 [5.86 - 7.10]	262,103
	All admissions 2019/20		6.31 [5.86 - 6.76]	448,138
	Influenza admissions 2019/20		14.85 [10.15 - 19.55]	4,177
Sickle Cell Disease	COVID-19		0.05 [-1.16 - 1.27]	2,891
	PIMS-TS		36.15 [-19.02 - 91.32]	262
	Other pandemic year admissions		1.55 [0.90 - 2.20]	244,932
	All admissions 2019/20		2.61 [1.74 - 3.48]	422,527
	Influenza admissions 2019/20		0.33 [-2.04 - 2.71]	3,733
Trisomy 21	COVID-19		18.61 [8.26 - 28.96]	2,990
	Other pandemic year admissions		4.72 [3.78 - 5.67]	244,428
	All admissions 2019/20		5.07 [4.27 - 5.87]	422,074
	Influenza admissions 2019/20		7.02 [-0.12 - 14.15]	3,723