Deaths in Children and Young People in England following SARS-CoV-2 infection during the first pandemic year: an observational study

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Abstract

SARS-CoV-2 infection is rarely fatal in children and young people (<18 years, CYP), but quantifying the risk of death is challenging because CYP are often infected with SARS-CoV-2 without exhibiting any or minimal symptoms. To distinguish between CYP who died as a result of SARS-CoV-2 infection from those who died of another cause but were coincidentally infected with the virus, we undertook a clinical review of all CYP deaths with a positive SARS-CoV-2 test from March 2020 to February 2021. The predominant SARS-CoV-2 variants were wild-type and alpha. Here we show of 12,023,568 CYP living in England, 3105 died, including 61 who were SARS-CoV-2 positive. Of these, 25 were due to SARS-CoV-2 infection (mortality rate, 2 per million), including 22 due to COVID-19, the clinical disease associated with SARS-CoV-2 infection, and three due to Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). 99.995% of CYP with a positive SARS-CoV-2 test survived. CYP aged >10 years, Asian and Black ethnic backgrounds, and comorbidities were over-represented in SARS-CoV-2 related deaths compared to other CYP deaths. These results are important for guiding decisions on shielding and vaccinating children. New variants may have different mortality risks and should be evaluated in a similar way.

Main text

Introduction

Identifying Children and Young People (CYP) at risk of severe illness and death following SARS-CoV-2 infection is essential to guide families, clinicians and policy makers about future shielding policies, school attendance, novel therapeutic agents and vaccine prioritisation.

SARS-CoV-2 infection is usually mild and asymptomatic in CYP.[1,2,3] Therefore, CYP have comprised a very low proportion of all hospitalisations and deaths from COVID-19 globally.[4] The clinical manifestations of COVID-19 in CYP are different to those amongst adults.[1] While many CYP present with the typical fever, cough and shortness of breath, they also present with broader non-specific symptoms including abdominal pain, nausea, headache and sore throat.[1,3] This, in combination with a mild or asymptomatic phenotype,[2] provides a challenge for describing how SARS-CoV-2 directly affects CYP.

Severe illness and death associated with SARS-CoV-2 in CYP is rare and can be due to either acute COVID-19 or Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS).[2.5] PIMS-TS, also called Multi-System Inflammatory Syndrome in Children (MIS-C), is a rare syndrome characterised by persistent fever, inflammation (neutrophilia, lymphopaenia, and raised CRP) and evidence of single or multi-organ dysfunction that may occur concurrently or after infection.[6] As death from acute COVID-19 or PIMS-TS amongst CYP is extremely rare[4,7,8] those that have died have been poorly characterised.[9] Further, it remains unclear to what extent these rare deaths relate directly to the pathological processes of COVID-19 or whether CYP who died from alternative causes were coincidentally SARS-CoV-2 positive around the time of death. This issue is made more difficult by the very high prevalence of asymptomatic infection at times of high prevalence, with reported prevalence up to 4-6% of UK CYP during December 2020.[10] The distinction between those who died of SARS-CoV-2 infection and those who died of an alternative cause with a coincidental positive SARS-CoV-2 test, is important for understanding which CYP are truly at higher risk for severe disease or death.

To answer this important question required detailed examination of all deaths in a large population, going beyond simple cause of death registration, to review the contribution of SARS-CoV-2 to death. We used detailed clinical data in the National Child Mortality Database (NCMD),[11] a comprehensive and unique mandatory national dataset of deaths <18 years of age, to review the contribution of SARS-CoV-2 to death.

If higher risk groups are identified, they may benefit from vaccination and/or protective 'shielding' at times of high prevalence, whereas 'shielding' based upon erroneous assumptions of vulnerability is likely to cause significant secondary harms e.g. impact of not attending school, restrictive or reduced socialising affecting both development and mental health. Similarly, risks from the disease need to be weighed against potential risks of vaccination in informing vaccination policy. Therefore this study aimed to:

1. Quantify the number of CYP who died of SARS-CoV-2 by differentiating between CYP who died of SARS-CoV-2 and those who died of an alternative cause with a coincidental positive SARS-CoV-2 test

2. Assess the clinical and demographic characteristics of the CYP who died of SARS-CoV-2 in comparison to CYP deaths from all other causes during the first pandemic year

Results

Between March 2020 and February 2021, 3105 CYP in England died of all causes. Of these, 61 CYP had a positive SARS-CoV-2 test and 3044 died from all other causes.

Clinical records of the 61 CYP who died with a positive SARS-CoV-2 test were reviewed to identify if SARS-CoV-2 contributed to death. This process initially included identifying whether SARS-CoV-2 was listed as 1a (the direct cause of death) on the Certificate of Cause of Death and whether the clinical course described was typical of SARS-CoV-2 infection. In these circumstances, the classification 'SARS-CoV-2 clearly contributed to death' was applied. In England, the Certificate of Cause of Death is set out in two parts.[12] Part 1a is the immediate, direct cause of death. The sequence of events or conditions that led to the death are then listed as 1b and 1c (if necessary).[12]

If the role of SARS-CoV-2 in contributing to death was not clearly apparent, each case underwent review by three independent senior clinical experts in relevant fields (General Paediatrics, Neonatology and Paediatric Intensive Care) who were asked to classify each case. Definitions for each category and the detail behind the process is outlined in the supplementary material and in Figure 1.

25 (41%) of the 61 CYP died of SARS-CoV-2 including 22 with acute COVID-19 and three with PIMS-TS. In the other 36 (59%) of the 61 test-positive CYP, SARS-CoV-2 did not contribute to death (Table 1, Figure 1, Figure 2).

There were an estimated 469,982 CYP infected with SARS-CoV-2 in England from March 2020 to February 2021, giving an infection fatality rate of 5 per 100,000 CYP (0·005%) and, based on a population of 12,023,568, a mortality rate of 2 per million CYP (0·0002%).[13]

Demographics
Table 1, Extended Data Figure 1, Extended Data Figure 2
There were small amounts of missing demographic data for the reference population (2.3% sex, 10.6% ethnicity and 0.6% deprivation – see Table 1) but there was no missing demographic data for the 25 CYP who died of SARS-CoV-2.

CYP who died of SARS-CoV-2 (n=25) were older than those who died from all other causes (n=3080) in the same time period. 18/25 (72%) young people who died of SARS-CoV-2 were aged 10 years or over, compared to 19% in the deaths from all other causes (chi-squared 59·7, p <0·001). All three deaths in CYP who died of PIMS-TS were aged 10-14 years. Of interest, specific to vaccination policy in the UK, there were 8 deaths in young people aged 12-15 years. The sex distribution was equally split between males and females (12 (48%) and 13 (52%) respectively) and did not differ from the deaths from all other causes (chi-squared2 0·64, p=0·28). A greater proportion of CYP from an Asian (36% compared to 16%) and Black (20% compared to 8%) ethnicity died of SARS-CoV-2 compared to deaths from all other causes (chi-squared 17·9, p<0·001). The three CYP who died of PIMS-TS were from different ethnic groups. There was no significant difference in the deprivation categories

between CYP who died of SARS-CoV-2 and deaths from all other causes (chi-squared 0·35, p=0·99) although more CYP from more deprived areas died in both groups.

The mortality rate in CYP who died of SARS-CoV-2 was 0·2 per 100,000 (95%CI 0·1-0·3) compared to 25·5 per 100,000 (95%CI 24·7-26·5) for all other causes of death. Although the proportion of CYP from Asian and Black ethnic groups who died of SARS-CoV-2 was higher, their absolute risk of death from SARS-CoV-2 was still extremely low at 0·6 per 100,000 (95%CI 0·3-1·1) and 0·8 per 100,000 (95%CI 0·3-1·8) respectively. Similarly, the proportion of CYP aged 10-14 years and 15-17 years who died of SARS-CoV-2 was higher than the proportion of CYP in the same age categories who died of all other causes. However, their absolute risk of death from SARS-CoV-2 was still extremely low at 0·3 per 100,000 (95%CI 0·1-0·5) and 0·5 (95%CI 0·2-0·9) per 100,000 respectively.

Co-morbidities

A similar proportion of the 25 CYP who died of SARS-CoV-2 (n=19, 76%) and the 3080 deaths from all other causes (n=2267, 74%) (chi-squared 0·004, p=0·60) had a chronic underlying health condition (Table 2, Table 3). Significantly more CYP who died of SARS-CoV-2 had a life-limiting condition (n=15, 60%) compared to deaths from all other causes (n=988, 32%) (chi-squared 8·5, p=0·005). 64% (n=16) of the 25 CYP who died of SARS-CoV-2 had comorbidities in two or more body systems compared to 45% (n=1373) of the CYP who died from all other causes (chi-squared 5·5, p=0·14).

Six (24%) of the 25 CYP who died of SARS-CoV-2 appeared to have no underlying health conditions similar to 24% (729 of the 3080 CYP) who died of all other causes. These six deaths included two CYP who died of PIMS-TS.

Neurological conditions were the commonest comorbidity in both the CYP who died of SARS-CoV-2 (n=13/25, 52%) and the CYP who died of all other causes (n=1218/3080, 40%; chi-squared 1·6, p=0·29). The chronic disease coding list used to identify neurological conditions included mental health and learning disability related codes. All 13 CYP who died of SARS-COV-2 with a neurological comorbidity had complex neurodisability due to a combination of an underlying genetic or metabolic condition, hypoxic ischaemic events or prematurity. Eight (32%) of the 13 CYP who had a neurological comorbidity also had a respiratory comorbidity, including five who required home respiratory support; four with non-invasive ventilation or high flow oxygen and one with low flow oxygen. There were zero CYP who died of SARS-CoV-2 that were invasively home ventilated. There was one death in a young person with a tracheostomy required for airway patency.

Amongst the 25 CYP who died of SARS-CoV-2 there was one child with each of the following comorbidities; congenital cardiac, oncological, obesity (under endocrinology) and complications of prematurity. There were two CYP who died with a haematological comorbidity.

There were no deaths in CYP with the following conditions:

- An isolated respiratory condition e.g. cystic fibrosis or asthma (three of the CYP with complex neurodisability had a historic diagnosis of asthma, however the asthma diagnosis was not considered to contribute to death).
- Type 1 diabetes
- Trisomy 21
- Isolated diagnosis of epilepsy
- A mental health disorder which caused or contributed to death.

There were CYP with asthma and epilepsy who died of SARS-CoV-2 infection. However, all of these deaths occurred in CYP with other underlying health conditions, rather than as a single diagnosis (Figure 3).

The estimated mortality rate for CYP who died of SARS-CoV-2 with a life-limiting condition was 11·5 per 100,000 (95%CI 5·6-21·2) compared to 1,124 per 100,000 (95%CI 1054-1197) for all other causes of death. Although the proportion of CYP with life-limiting neurodisability who died of SARS-CoV-2 was higher, their absolute risk of death was 88·9 per 100,000 (95%CI 47·3-152) compared to 2,441 per 100,000 (95% CI 2,194-2,707) in CYP with life-limiting neurodisability who died of all other causes.

Place of death
Nine (36%) of the 25 CYP who died of SARS-CoV-2, died within a Paediatric Intensive Care Unit and four died on a hospital ward. The remaining 12 CYP died either at home (unexpected (n=6) or expected (n=2)) or in the Emergency Department (n=4). There were five deaths in CYP with advance care plans in place to provide hospital ward level care rather than escalate to intensive care.

Time interval between positive SARS-CoV-2 test and death
23 CYP died of SARS-CoV-2 within 28 days of a positive SARS-CoV-2 test, 21 of which occurred within seven days of a positive test. The maximum time between death and a positive SARS-CoV-2 test was 45 days.

The 3044 CYP who died and did not have a positive SARS-CoV-2 test, would have only had a SARS-CoV-2 test in the following circumstances; asymptomatic lateral flow tests performed for education or social activities (note this is hugely variable), symptoms consistent with acute SARS-CoV-2 infection, hospital admission, unexpected death or post-mortem examination. Therefore, not all of the 3044 CYP who died from other causes would have been tested for SARS-CoV-2. However none of them had a positive SARS-CoV-2 test because we included all CYP who tested positive at any time point during the pandemic (n=61) and zero positive tests were excluded from the study.

Discussion
We used a high quality unique national mortality dataset linked to national hospital and SARS-CoV-2 PHE testing data, in-conjunction with clinical review, to identify 25 CYP who died of SARS-CoV-2 infection during the first pandemic year. This corresponds to 2 deaths per million across the CYP population in England. We estimated the infection fatality rate is 5 per 100,000 indicating >99·995% of CYP recover from SARS-CoV-2 infection. SARS-CoV-2 contributed to 0·8% of the 3105 deaths from all causes. During the same time period studied there were 124 deaths from suicide and 268 deaths from trauma, emphasising COVID-19 is rarely fatal in CYP.

This is the first study to differentiate between CYP who have died of SARS-CoV-2 infection rather than died with a positive SARS-CoV-2 test as a coincidental finding. Our result is 60% lower than the figures derived from positive tests thereby markedly reducing the estimated number of CYP who are potentially at risk of death during this pandemic[14].

The CYP who died of SARS-CoV-2 were more likely to be teenagers than younger children, suggesting a continuum of risk increasing through the life-course from infancy to older adult life[15]. Higher proportions of Asian and Black CYP died of SARS-CoV-2 compared to all other causes of death, although deaths were still extremely rare. The three CYP who died of PIMS-TS were all aged 10-14 years, two were male, all were from different ethnic groups and two did not have evidence of an underlying health condition.

The reason for ethnic differences may be due to biological predisposition and/or access to care. Of note, the differences persist when controlling for deprivation.[16] These findings support those found in adult studies.[15,17]

Our findings emphasise the importance of underlying comorbidities as the main risk factor for death, as 76% had chronic conditions, 64% had multiple comorbidities, and 60% had life-limiting conditions. The comorbidity group at highest risk were those with complex neurodisability, who comprised 52% of all deaths in CYP who died of SARS-CoV-2. CYP with combined neurodisability and respiratory conditions (8 of the 13 deaths with neurodisability) may be at particularly high risk. CYP with a life-limiting neurodisability have a higher background mortality rate than the general population.[18Error! Bookmark not defined.] There are around 500 deaths annually in this group and therefore SARS-CoV-2 contributed to only 3% during the pandemic. Similarly, for all other comorbidity groups, those who died of SARS-CoV-2 represented a very small proportion of all deaths during the pandemic year. It is important to note we observed no deaths in groups who have been considered at higher risk of respiratory infections, such as CYP with asthma, cystic fibrosis, type 1 diabetes or trisomy 21.

The inclusion of trauma as a chronic condition relates to the broad definition of chronic conditions used in this work to ensure optimal capture. The chronic condition definition (see supplementary information) includes any health problem requiring follow up services in more than 50% of cases, and follow up includes use of support services such as physiotherapy. There is a subcategory of skeletal injuries/amputations which accounts for these trauma codes which are historic but chronic in nature. The high number of CYP with ENT conditions is due to a high proportion of CYP with neurological and/or respiratory conditions having ENT conditions and does not relate to CYP with isolated ENT conditions. It also includes CYP with a tracheostomy.

Six CYP who died of SARS-CoV-2 had no evidence of an underlying health condition. This contrasts with other studies which have only reported deaths in CYP who have comorbidity.[7,19] It is possible, due to the hospital data only being available for the last five years, that some CYP may have had a comorbidity that was not identified in this linkage. It is also possible that CYP in our study had an undiagnosed genetic predisposition to severe disease with SARS-CoV-2 infection.[20]

Our findings extend previous more limited reports on deaths due to SARS-CoV-2 in the UK.[Error! Bookmark not defined.,Error! Bookmark not defined.,19] The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) study reported six deaths from 651 admissions across 138 hospitals up to July 2020.[19] All six CYP had “profound comorbidity” which included neurodisability, extreme prematurity, malignancy and sepsis; three were infants under 28 days of age and three aged 15-18 years.[19] The methodology in our study enabled demonstration that zero neonates died of SARS-CoV-2 highlighting the value of having real-time, complete, mortality surveillance for CYP, with linkage to virology data and the detailed clinical review we undertook to determine the role of SARS-CoV-2 in death.

The current UK advice on those defined as “clinically extremely vulnerable” was initially extrapolated from adult risk and it remains very cautious.[14] Even taking into consideration the effect of shielding (as both adults and CYP shielded at times during this period) the risk of serious outcomes from SARS-CoV-2 for under 18’s remains extremely low. The risk of removal of CYP from their normal activities across education and social events may prove a greater risk than that of SARS-CoV-2 itself.[21]

Limitations

The SARS-CoV-2 virus strains circulating at the time of this review were wild-type and the alpha variant from November 2020. These data are specific to the time period studied and prior to the advent of the delta variant.

The data analysed in this study largely relied upon the quality of the data entered through the NCMD death reporting process. Data completeness was variable, depending on stage of the child death

review process. Where possible, we overcame this through discussion with reporting clinicians and data linkage. Rapid data linkage methods were undertaken utilising NHS number alone so this may have resulted in some CYP not being matched to their hospital data.

Eight of the CYP who died of SARS-CoV-2 had a non-congenital cardiac condition recorded – despite our attempts to modify the ICD-10 coding lists to account for this, due to the complexity of these cases some of these conditions may have been as a result of COVID-19 rather than pre-existing chronic conditions.

Even though we undertook rigorous clinical review there may still have been a potential for misclassification of deaths in this study. All sudden and unexpected deaths were tested for SARS-CoV-2 as part of the amended Joint Agency Response policy from March 2020.[22] However not all community deaths will have been routinely tested.

As there is no diagnostic test for PIMS-TS and coding was a challenge it is possible that there may be omissions due to the methods of diagnosis and reporting.

The mortality rate calculations used data from the office of national statistics for estimated number of children by age in England during mid-2019.[13] There is a paucity of accurate data on the number of children who have had SARS-CoV-2 testing, impacting the accuracy of the infection fatality rate calculation.

Going forward, linkage of the NCMD to other national datasets will enable complete capture of co-morbidities in CYP. These findings are representative of the wild-type and alpha SARS-CoV-2 variant that were prevalent at the time of the study. It would be beneficial to repeat this for the subsequent 12 months (March 2021 – February 2022) to identify the effect of other variants (including delta) and vaccination.

Tables

Table 1 Demographic details for Children and Young People (CYP) who died between March 2020 to February 2021 from all causes, and the 61 CYP who died with a positive SARS-CoV-2 test, split by the likely cause of death.

All Deaths		All deaths March 2020 - February 2021 (n=3105)								
		Reference Population (n=3080) - All other causes of death					Died of COVID-19/PIMS-TS (n=25)			Comparison of frequencies*
		Died without positive test for SARS-CoV-2 (N=3044)		Incidental positive SARS-CoV-2 test at death (n=36)		Est Rate/100,000 person years (95%Poisson CI)				
		Number	Percentage	Number	Percentage		Number	Percentage	Est Rate/100,000 person years (95%Poisson CI)	P
		3044	100%	36	100%	25·5 (24·7-26·5)	25	100%	0·2 (0·1-0·3)	
Age	0 - 27 days	1388	45·6%	3	8·3%	289·3 (276·8-302·1)	0	0·0%	0·3 (0·0-11·0)	<0·001
	28 - 364 days	616	20·2%	11	30·6%		2	8·0%		
	1 - 4 years	281	9·2%	4	11·1%	10·4 (9·2-11·6)	0	0·0%	0·00 (-)	
	5 - 9 years	191	6·3%	4	11·1%	5·7 (4·9-6·6)	5	20·0%	0·1 (0·0-0·3)	
	10 - 14 years	252	8·3%	6	16·7%	7·6 (6·7-8·6)	9	36·0%	0·3 (0·1-0·5)	
	15 - 17 years	316	10·4%	8	22·2%	17·3 (15·5-19·3)	9	36·0%	0·5 (0·2-0·9)	
Sex	Female	1667	54.8%	18	50·0%	22·4 (21·2-23·7)	12	48·0%	0·2 (0·1-0·4)	0·28
	Male	1308	43.0%	18	50·0%	27·1 (25·9-28·5)	13	52·0%	0·2 (0·1-0·3)	
	Missing	69	2.3%	-	-	-	-	-	-	
Ethnicity	Asian or Asian British	471	15.5%	10	27.8%	31·3 (28·6-34·2)	9	36·0%	0·6 (0·3-1·1)	<0·001
	Black or Black British	241	7.9%	4	11.1%	37·8 (33·2-42·9)	5	20·0%	0·8 (0·3-1·8)	
	Mixed	169	5.6%	1	2.8%	23·3 (19·9-27·1)	4	16·0%	0·5 (0·1-1·4)	
	Other	74	2.4%	0	0.0%	49·8 (39·1-62·5)	0	0·0%	0·00 (-)	
	White	1764	58.0%	20	55.6%	19·7 (18·8-20·6)	7	28·0%	0·1 (0·0-0·2)	
	Missing	325	10.7%	1	2.8%	-	-	-	-	
Deprivation	1	985	32.4%	15	41·7%	34·8 (32·7-37·0)	9	36·0%	0·3 (0·1-0·6)	0·99

Category	2	687	22.6%	8	22·2%	27·9 (25·9-30·1)	6	24·0%	0·2 (0·1-0·5)	
	3	615	20.2%	6	16·7%	27·4 (25·3-29·6)	5	20·0%	0·2 (0·1-0·5)	
	4	402	13.2%	3	8·3%	18·7 (16·9-20·6)	3	12·0%	0·1 (0·0-0·4)	
	5	337	11.1%	4	11·1%	15·3 (13·8-17·1)	2	8·0%	0·1 (0·0-0·3)	
	Missing	18	0.6%	-	-	-	-	-	-	

Table 1 demonstrates the demographic details for the CYP who died of all causes and the CYP who died of SARS-CoV-2.
*The group of CYP who died of SARS-CoV-2 were compared to CYP who died from all other causes using summary statistics and differences between groups were compared using two sided chi-squared or Fishers exact test if small numbers. No adjustment for multiple testing was undertaken.
Values are n(%) or median (IQR) as appropriate.

Table 2 Co-morbidity details for Children and Young People (CYP) who died between March 2020 and February 2021 from all causes, and the 61 CYP who died with a positive SARS-CoV-2 test, split by the likely cause of death.

All deaths		All deaths March 2020 - February 2021 (n=3105)						
		Reference Population (n=3080)				Died of COVID-19/PIMS-TS (n=25)		Comparison of frequencies*
		All causes (n=3044)		Incidental positive SARS-CoV-2 test at death(n=36)				
		Number	Percentage	Number	Percentage	Number	Percentage	p
Life-limiting condition	Yes	974	32·0%	14	38·9%	15	60·0%	0·005
	No	2027	66·6%	22	61·1%	10	40·0%	
Chronic condition	Yes	2238	73·5%	29	80·6%	19	76·0%	0·6
	No	716	23·5%	7	19·4%	6	24·0%	
Chronic Condition Details	Cardiology (Non-congenital)	458	15·0%	8	22·2%	8	32·0%	0·02
	Cardiology (Congenital)	667	21·9%	10	27·8%	1	4·0%	0·03
	Dermatology	14	0·5%	0	0·0%	0	0·0%	-
	Endocrine (including Obesity)	29	1·0%	1	2·8%	1	4·0%	0·22
	ENT (including Tracheostomy)	70	2·3%	5	13·9%	10	40·0%	<0·001
	Gastroenterology	467	15·3%	18	50·0%	5	20·0%	0·56
	Genetic	88	2·9%	1	2·8%	8	32·0%	<0·001
	Haematological	287	9·4%	12	33·3%	2	8·0%	0·81
	Immunological	19	0·6%	2	5·6%	1	4·0%	0·16
	Infectious disease	15	0·5%	0	0·0%	0	0·0%	-
	Metabolic	181	5·9%	7	19·4%	4	16·0%	0·07
	Musculoskeletal	142	4·7%	5	13·9%	4	16·0%	0·03
	Neurological	1194	39·2%	24	66·7%	13	52·0%	0·29
	Oncology	190	6·2%	8	22·2%	1	4·0%	0·51
	Renal	300	9·9%	6	16·7%	2	8·0%	0·74
	Reproductive system	9	0·3%	1	2·8%	0	0·0%	-
	Respiratory	474	15·6%	10	27·8%	12	48·0%	<0·001
	Rheumatology	4	0·1%	1	2·8%	0	0·0%	-

	Trauma	12	0·4%	2	5·6%	0	0·0%	-

All deaths		Reference Population (n=3080)				Died of COVID-19/PIMS-TS (n=25)		Comparison of frequencies*
		All causes (n=3044)		Incidental positive SARS-CoV-2 test at death(n=36)				
		Number	Percentage	Number	Percentage	Number	Percentage	p
Number of comorbidities	0	716	23·5%	13	21·3%	6	24·0%	0·14
	1	906	29·8%	7	11·5%	3	12·0%	
	2 or more	1332	43·8%	41	67·2%	16	64·0%	
	Unknown	90	3·0%	0	0·0%	0	0·0%	
	Total	3044	100·0%	61	100·0%	25	100·0%	-
Comorbidity combinations	Neurological & Respiratory	318	10·4%	17	27·9%	8	32·0%	<0·001
	Neurological & Cardiology	559	18·4%	15	24·6%	3	12·0%	0·61
	Respiratory & Cardiology	270	8·9%	12	19·7%	3	12·0%	0·49
Single diagnoses	Asthma**	58	1·9%	5	8·2%	3	12·0%	0·02
	Type 1 Diabetes	9	0·3%	0	0·0%	0	0·0%	-
	Epilepsy**	199	6·5%	7	11·5%	7	28·0%	<0·001
	Sickle cell disease	1	0·0%	1	1·6%	1	4·0%	0·02
	Trisomy 21	38	1·2%	0	0·0%	0	0·0%	-

Table 2 demonstrates the co-morbidity details for the CYP who died of all causes and the CYP who died of SARS-CoV-2.
*The group of CYP who died of SARS-CoV-2 were compared to CYP who died from all other causes using summary statistics and differences between groups were compared using two sided chi-squared or Fishers exact test if small numbers. No adjustment for multiple testing was undertaken.

**There were zero deaths in CYP with an isolated diagnosis of asthma or epilepsy. All the deaths in CYP with asthma or epilepsy had an additional neurological comorbidity (see Figure 3).

Table 3: Estimated mortality rates by selected diagnostic groups for Children and Young People who died of SARS-CoV-2 and CYP who died of all other causes

	Estimated population at risk	Reference Population, all other causes (n=3080)		Died of COVID-19/PIMS-TS (n=25)	
		Number	Est Rate/100,000 person years (95%Poisson CI)	Number	Est Rate/100,000 person years (95%Poisson CI)
All children	12,118,268[13]	3080	25·4 (24·5,26·3)	25	0·2 (0·1,0·3)
Oncology	1,065[23]	137	12864 (10800,15207)	1	93·9 (2·4,523·2)
Life-limiting Neurodisability	14,626[18]	357	2441 (2194,2707)	13	88·9 (47·3,152·0)
Life-limiting condition	86,625[18]	974	1124 (1054,1197)	15	11·5 (5·6,21·2)
Cardiology (Congenital)	90,000[24]	458	508·9 (463·3,557·7)	1	8·9 (3·8,17·5)
Epilepsy**	90,000[25]	199	214 (185,246)	7	7·5 (3·0,15·5)
Asthma**	1,100,000[26]	58	5·3 (4·0,6·8)	3	0·3 (0·06,0·8)

Table 3 demonstrates the mortality rate for all CYP and for all deaths within selected diagnostic groups: Oncology, Life-limiting neurodisability, Life-limiting condition, Cardiology (Congenital), Epilepsy, Asthma.

**There were zero deaths in CYP with an isolated diagnosis of asthma or epilepsy. All the deaths in CYP with asthma or epilepsy had an additional neurological comorbidity (see Figure 3)

Figure legends/captions (for main text figures)

Figure 1 is a flow diagram demonstrating the approach that was used to determine if SARS-CoV-2 contributed to death or if it was a co-incidental finding. This was applied to all Children and Young People (CYP) who died and had a positive SARS-CoV-2 test. The numbers are included at each representative stage.

Figure 2 is a graph demonstrating the cumulative number of deaths for all Children and Young People (CYP) who died with a positive SARS-CoV-2 test in the study period (March 2020 to February 2021). It compares the number of CYP who died of SARS-CoV-2, the number of CYP who died with a positive SARS-CoV-2 test and the number of CYP who died who died of all other causes.

Figure 3 is an upset plot to visualise the intersections between the single diagnosis codes asthma and epilepsy. For individual Children and Young People with epilepsy or asthma it highlights their other comorbidities with a black circle, demonstrating these single diagnosis codes did not occur in isolation.

Extended Data Figure 1 is a bar chart demonstrating the age group of Children and Young People (CYP) who died of SARS-CoV-2 (n=25) compared to the age group of CYP deaths from all other causes (n=3080).

Extended Data Figure 2 is a bar chat demonstrating the ethnic group of Children and Young People (CYP) who died of SARS-CoV-2 (n=25) compared to the ethnic group of CYP deaths from all other causes (n=3080).

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Methods

Population

The cohort investigated in this study is all CYP <18 years of age, who died in England between 1st March 2020 and the 28th February 2021.[1] The aim of this study was to identify CYP in which SARS-CoV-2 contributed to death, i.e. they died of SARS-CoV-2 infection.

Ethics approval was granted from Central Bristol NHS Research and Ethics Committee (REC). Informed consent was not obtained for use of this data. The NCMD has a legal basis to collect data without consent (see supplementary information).[2] Current Control Of Patient Information (COPI) regulations provide a legal basis for linking NCMD data with SUS data without consent[3]. Further detail is provided in the Supplementary information.

A statistical risk assessment for this study determined that whilst data is anonymised, identification of individuals may be possible. However, the risk of attribute details being disclosed was low and the public benefit of reporting these small numbers outweighed this risk. We have minimised this risk by providing data that is two dimensional rather than three dimensional e.g. we have provided the number of CYP in each age or ethnicity category rather than providing linked comorbidity and demographic details for each CYP. Given the sensitive nature of these data and our awareness that clinicians and families may recognise personal experience, we met with a clinician or professional involved in the care of each child or young person who died of SARS-CoV-2 infection. We asked the respective clinician or professional to communicate this work directly with the families.

Data Collection

The NCMD is a mandatory system that records all deaths in CYP <18 years of age in England, since it began in April 2019[1] and includes demographic and clinical data of the events leading up to death.
In this analysis, demographic details included age (coded as 0-27 days, 28-364 days, 1-4 years, 5-9 years, 10-14 years and 15-17 years), sex, ethnicity (coded as Asian or Asian British, Black or African or Caribbean or Black British, Mixed, Multiple, Other (includes Arab and other ethnic groups) and White)[4] and deprivation (see supplementary information).[5,6]

Data linkage

To ensure comprehensive identification of comorbidities, NCMD data were linked to the preceding five years (March 2015 onwards) of national admitted patient care Secondary Uses Service (SUS) data for England[7] and to the national Paediatric Intensive Care Audit Network (PICANet) data. A validated list of ICD-10 codes was used to identify CYP with chronic co-morbidities[8] and life-limiting conditions[9] (see supplementary information). Of note, the chronic disease list for cardiac conditions was modified to remove 'I46-Cardiac Arrest' and 'I51-Complications and ill-defined descriptions of heart disease' as these are acute presentations of cardiac disease and likely to represent PIMS-TS rather than pre-existing comorbidity. We also identified CYP with chronic comorbidities in two or more body systems and with the following single diagnoses: asthma, diabetes, epilepsy, sickle cell disease and trisomy 21. These single diagnoses were identified as common long-term conditions in CYP and from single case studies, clinicians, patient groups and adult studies speculated to be at increased risk from SARS-CoV-2.[10,11]

Data availability statement

Data that has been used for this study is not publicly available because it is highly sensitive information available at identifiable patient level because of small numbers. The analysis was performed in Microsoft Excel using basic count functions to identify CYP within each category. Statistical analysis was performed in Stata using the data within Table 1 and Table 2.

SARS-CoV-2 Data

During the pandemic, the NCMD was linked by NHS number to Public Health England (PHE) Pillar 1 and Pillar 2 testing data[12] to identify all CYP who died with a positive SARS-CoV-2 test. Pillar 1 testing occurs in health and care settings, while Pillar 2 testing occurs in the community,[12] both started in March 2020. The NCMD contributed to modification of the protocol for sudden unexpected deaths in CYP to include post-mortem testing for SARS-CoV-2.[13] All CYP who died with a positive SARS-CoV-2 test were included, regardless of the time interval between positive test and death. This is different to the definition used for reporting adult deaths to ensure all potential cases were identified for review and to optimise capture of possible PIMS-TS cases. In addition, the NCMD coding team identified potential cases of PIMS-TS (see supplementary material).

Identifying CYP who died of SARS-CoV-2

Clinical records of all CYP who died with a positive SARS-CoV-2 test were reviewed to identify if SARS-CoV-2 clearly, probably, possibly or unlikely contributed to death. This process initially included identifying whether SARS-CoV-2 was listed as 1a (the direct cause of death) on the Certificate of Cause of Death and whether the clinical course described was typical of SARS-CoV-2 infection. In these circumstances, the classification 'SARS-CoV-2 clearly contributed to death' was applied. In England, the certificate of cause of death is set out in two parts.[14] Part 1a is the immediate, direct cause of death. The sequence of events or conditions that led to the death are then listed as 1b and 1c (if necessary). Other disease, injuries, conditions or events that contributed to death but were not part of the direct sequence are then documented in part 2.[14]

If it was not clearly apparent, each case underwent review by three independent senior clinical experts in relevant fields (General Paediatrics, Neonatology and Paediatric Intensive Care) who were asked to classify each case. Each senior clinical expert was blinded to the opinion of the other reviewers. Definitions for each category and the detail behind the process is outlined in the supplementary material and Figure 1.

Statistical Analysis

The group of CYP who died of SARS-CoV-2 were compared to CYP who died from all other causes using summary statistics and differences between groups were compared using two sided chi-squared or Fishers' Exact test if small numbers. The comparator cohort, death from all other causes, included CYP who tested positive for SARS-CoV-2, but died of another cause. Due to a small amount of missing data, multiple imputation was not undertaken.

The absolute risk of death was calculated for the whole population and for demographic groups in which denominator data were available. The quality of available data on the number of CYP in the population with comorbidities was variable. We have used estimates for comorbidity groups, where we have enough confidence in the data, to derive estimated absolute risk. This data came from a range of sources and is referenced in Table 3.

Infection fatality rate was calculated using the number of CYP infected with SARS-CoV-2 during the same time period (March 2020 to February 2021) estimated through PHE modelling data.[15] This was chosen rather than the absolute number of positive SARS-CoV-2 tests as CYP may test positive more than once, and many CYP were not tested in the first wave of the pandemic. Mortality rate was calculated using a population of 12,023,568 CYP living in England[16] during the study year.

This study has been reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guideline for reporting observational studies'.[17]

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Author Contributions Statement
Study Design: CS, DO, RH, JW, ML, MC, DH, SL, ED, PD, SK, EW, KL, RV, LF.
Data collection and analysis: CS, DO, LF, KL
Data interpretation: CS, DO, EH, JW, ML, MC, DH, SL, ED, PD, SK, EW, KL, RV, LF. Reviewed underlying data CS, DO, LF
First draft: CS
Review and editing: CS, DO, RH, JW, ML, MC, DH, SL, ED, PD, SK, EW, KL, RV, LF.

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