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

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32 Abstract

33 SARS-CoV-2 infection is rarely fatal in children and young people (<18 years, CYP), but quantifying
34 the risk of death is challenging because CYP are often infected with SARS-CoV-2 without exhibiting
35 any or minimal symptoms. To distinguish between CYP who died as a result of SARS-CoV-2 infection
36 from those who died of another cause but were coincidentally infected with the virus, we undertook
37 a clinical review of all CYP deaths with a positive SARS-CoV-2 test from March 2020 to February
38 2021. The predominant SARS-CoV-2 variants were wild-type and alpha. Here we show of 12,023,568
39 CYP living in England, 3105 died, including 61 who were SARS-CoV-2 positive. Of these, 25 were due
40 to SARS-CoV-2 infection (mortality rate, 2 per million), including 22 due to COVID-19, the clinical
41 disease associated with SARS-CoV-2 infection, and three due to Paediatric Inflammatory Multisystem
42 Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS). 99.995% of CYP with a positive SARS-
43 CoV-2 test survived. CYP aged >10 years, Asian and Black ethnic backgrounds, and comorbidities
44 were over-represented in SARS-CoV-2 related deaths compared to other CYP deaths. These results
45 are important for guiding decisions on shielding and vaccinating children. New variants may have
46 different mortality risks and should be evaluated in a similar way.

47

48

49 Main text

50 Introduction

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

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

61 Severe illness and death associated with SARS-CoV-2 in CYP is rare and can be due to either acute
62 COVID-19 or Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-
63 2 (PIMS-TS).^{2,5} PIMS-TS, also called Multi-System Inflammatory Syndrome in Children (MIS-C), is a
64 rare syndrome characterised by persistent fever, inflammation (neutrophilia, lymphopaenia, and
65 raised CRP) and evidence of single or multi-organ dysfunction that may occur concurrently or after
66 infection.⁶ As death from acute COVID-19 or PIMS-TS amongst CYP is extremely rare^{4,7,8} those that
67 have died have been poorly characterised.⁹ Further, it remains unclear to what extent these rare
68 deaths relate directly to the pathological processes of COVID-19 or whether CYP who died from
69 alternative causes were coincidentally SARS-CoV-2 positive around the time of death. This issue is
70 made more difficult by the very high prevalence of asymptomatic infection at times of high
71 prevalence, with reported prevalence up to 4-6% of UK CYP during December 2020.¹⁰ The distinction
72 between those who died of SARS-CoV-2 infection and those who died of an alternative cause with a
73 coincidental positive SARS-CoV-2 test, is important for understanding which CYP are truly at higher
74 risk for severe disease or death.

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

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

- 86 1. Quantify the number of CYP who died of SARS-CoV-2 by differentiating between CYP who
87 died of SARS-CoV-2 and those who died of an alternative cause with a coincidental positive
88 SARS-CoV-2 test
- 89 2. Assess the clinical and demographic characteristics of the CYP who died of SARS-CoV-2 in
90 comparison to CYP deaths from all other causes during the first pandemic year

91 Results

92

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

95

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

103

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

109

110 25 (41%) of the 61 CYP died of SARS-CoV-2 including 22 with acute COVID-19 and three with PIMS-
111 TS. In the other 36 (59%) of the 61 test-positive CYP, SARS-CoV-2 did not contribute to death (Table
112 1, Figure 1, Figure 2).

113

114 There were an estimated 469,982 CYP infected with SARS-CoV-2 in England from March 2020 to
115 February 2021, giving an infection fatality rate of 5 per 100,000 CYP (0.005%) and, based on a
116 population of 12,023,568, a mortality rate of 2 per million CYP (0.0002%).¹³

117

118 *Demographics*

119 *Table 1, Extended Data Figure 1, Extended Data Figure 2*

120 There were small amounts of missing demographic data for the reference population (2.3% sex,
121 10.6% ethnicity and 0.6% deprivation – see Table 1) but there was no missing demographic data for
122 the 25 CYP who died of SARS-CoV-2.

123

124 CYP who died of SARS-CoV-2 (n=25) were older than those who died from all other causes (n=3080)
125 in the same time period. 18/25 (72%) young people who died of SARS-CoV-2 were aged 10 years or
126 over, compared to 19% in the deaths from all other causes (chi-squared 59.7, p <0.001). All three
127 deaths in CYP who died of PIMS-TS were aged 10-14 years. Of interest, specific to vaccination policy
128 in the UK, there were 8 deaths in young people aged 12-15 years. The sex distribution was equally
129 split between males and females (12 (48%) and 13 (52%) respectively) and did not differ from the
130 deaths from all other causes (chi-squared 2 0.64, p=0.28). A greater proportion of CYP from an Asian
131 (36% compared to 16%) and Black (20% compared to 8%) ethnicity died of SARS-CoV-2 compared to
132 deaths from all other causes (chi-squared 17.9, p<0.001). The three CYP who died of PIMS-TS were
133 from different ethnic groups. There was no significant difference in the deprivation categories

134 between CYP who died of SARS-CoV-2 and deaths from all other causes (chi-squared 0.35, p=0.99)
135 although more CYP from more deprived areas died in both groups.

136

137 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
138 25.5 per 100,000 (95%CI 24.7-26.5) for all other causes of death. Although the proportion of CYP
139 from Asian and Black ethnic groups who died of SARS-CoV-2 was higher, their absolute risk of death
140 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
141 (95%CI 0.3-1.8) respectively. Similarly, the proportion of CYP aged 10-14 years and 15-17 years who
142 died of SARS-CoV-2 was higher than the proportion of CYP in the same age categories who died of all
143 other causes. However, their absolute risk of death from SARS-CoV-2 was still extremely low at 0.3
144 per 100,000 (95%CI 0.1-0.5) and 0.5 (95%CI 0.2-0.9) per 100,000 respectively.

145

146 *Co-morbidities*

147 A similar proportion of the 25 CYP who died of SARS-CoV-2 (n=19, 76%) and the 3080 deaths from all
148 other causes (n=2267, 74%) (chi-squared 0.004, p=0.60) had a chronic underlying health condition
149 (Table 2, Table 3). Significantly more CYP who died of SARS-CoV-2 had a life-limiting condition (n=15,
150 60%) compared to deaths from all other causes (n=988, 32%) (chi-squared 8.5, p=0.005). 64% (n=16)
151 of the 25 CYP who died of SARS-CoV-2 had comorbidities in two or more body systems compared to
152 45% (n=1373) of the CYP who died from all other causes (chi-squared 5.5, p=0.14).

153

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

157

158 Neurological conditions were the commonest comorbidity in both the CYP who died of SARS-CoV-2
159 (n=13/25, 52%) and the CYP who died of all other causes (n=1218/3080, 40%; chi-squared 1.6,
160 p=0.29). The chronic disease coding list used to identify neurological conditions included mental
161 health and learning disability related codes. All 13 CYP who died of SARS-COV-2 with a neurological
162 comorbidity had complex neurodisability due to a combination of an underlying genetic or metabolic
163 condition, hypoxic ischaemic events or prematurity. Eight (32%) of the 13 CYP who had a
164 neurological comorbidity also had a respiratory comorbidity, including five who required home
165 respiratory support; four with non-invasive ventilation or high flow oxygen and one with low flow
166 oxygen. There were zero CYP who died of SARS-CoV-2 that were invasively home ventilated. There
167 was one death in a young person with a tracheostomy required for airway patency.

168

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

172

173 There were no deaths in CYP with the following conditions:

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

181

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

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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 pandemic¹⁴.

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 life¹⁵. 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}

236

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

248

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

257

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

263

264 Our findings extend previous more limited reports on deaths due to SARS-CoV-2 in the UK.Error!
265 Bookmark not defined.,Error! Bookmark not defined.,19 The International Severe Acute Respiratory and emerging
266 Infection Consortium (ISARIC) study reported six deaths from 651 admissions across 138 hospitals up
267 to July 2020.¹⁹ All six CYP had “profound comorbidity” which included neurodisability, extreme
268 prematurity, malignancy and sepsis; three were infants under 28 days of age and three aged 15-18
269 years.¹⁹ The methodology in our study enabled demonstration that zero neonates died of SARS-CoV-
270 2 highlighting the value of having real-time, complete, mortality surveillance for CYP, with linkage to
271 virology data and the detailed clinical review we undertook to determine the role of SARS-CoV-2 in
272 death.

273

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

279

280 Limitations

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

284

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

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

290

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

295

296 Even though we undertook rigorous clinical review there may still have been a potential for
297 misclassification of deaths in this study. All sudden and unexpected deaths were tested for SARS-
298 CoV-2 as part of the amended Joint Agency Response policy from March 2020.²² However not all
299 community deaths will have been routinely tested.

300

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

303

304 The mortality rate calculations used data from the office of national statistics for estimated number
305 of children by age in England during mid-2019.¹³ There is a paucity of accurate data on the number
306 of children who have had SARS-CoV-2 testing, impacting the accuracy of the infection fatality rate
307 calculation.

308

309 Going forward, linkage of the NCMD to other national datasets will enable complete capture of co-
310 morbidities in CYP. These findings are representative of the wild-type and alpha SARS-CoV-2 variant
311 that were prevalent at the time of the study. It would be beneficial to repeat this for the subsequent
312 12 months (March 2021 – February 2022) to identify the effect of other variants (including delta)
313 and vaccination.

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323 Tables

324 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
 325 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%	-	-	-	-	-	-	

326

327 Table 1 demonstrates the demographic details for the CYP who died of all causes and the CYP who died of SARS-CoV-2.

328 *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
329 were compared using two sided chi-squared or Fishers exact test if small numbers. No adjustment for multiple testing was undertaken.

330 Values are n(%) or median (IQR) as appropriate.

331

332 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
 333 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%	-

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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).

344 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
 345 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)

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

349 **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
 350 neurological comorbidity (see Figure 3)

351 Figure legends/captions (for main text figures)

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

356 Figure 2 is a graph demonstrating the cumulative number of deaths for all Children and Young
357 People (CYP) who died with a positive SARS-CoV-2 test in the study period (March 2020 to February
358 2021). It compares the number of CYP who died of SARS-CoV-2, the number of CYP who died with a
359 positive SARS-CoV-2 test and the number of CYP who died who died of all other causes.

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

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

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

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483 Methods

484 Population

485 The cohort investigated in this study is all CYP <18 years of age, who died in England between 1st
486 March 2020 and the 28th February 2021.¹ The aim of this study was to identify CYP in which SARS-
487 CoV-2 contributed to death, i.e. they died of SARS-CoV-2 infection.

488

489 Ethics approval was granted from Central Bristol NHS Research and Ethics Committee (REC).
490 Informed consent was not obtained for use of this data. The NCMD has a legal basis to collect data
491 without consent (see supplementary information).² Current Control Of Patient Information (COPI)
492 regulations provide a legal basis for linking NCMD data with SUS data without consent³. Further
493 detail is provided in the Supplementary information.

494

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

504

505 Data Collection

506 The NCMD is a mandatory system that records all deaths in CYP <18 years of age in England, since it
507 began in April 2019¹ and includes demographic and clinical data of the events leading up to death.

508 In this analysis, demographic details included age (coded as 0-27 days, 28-364 days, 1-4 years, 5-9
509 years, 10-14 years and 15-17 years), sex, ethnicity (coded as Asian or Asian British, Black or African
510 or Caribbean or Black British, Mixed, Multiple, Other (includes Arab and other ethnic groups) and
511 White)⁴ and deprivation (see supplementary information).^{5,6}

512

513 Data linkage

514 To ensure comprehensive identification of comorbidities, NCMD data were linked to the preceding
515 five years (March 2015 onwards) of national admitted patient care Secondary Uses Service (SUS)
516 data for England⁷ and to the national Paediatric Intensive Care Audit Network (PICANet) data. A
517 validated list of ICD-10 codes was used to identify CYP with chronic co-morbidities⁸ and life-limiting
518 conditions⁹ (see supplementary information). Of note, the chronic disease list for cardiac conditions
519 was modified to remove 'I46-Cardiac Arrest' and 'I51-Complications and ill-defined descriptions of
520 heart disease' as these are acute presentations of cardiac disease and likely to represent PIMS-TS
521 rather than pre-existing comorbidity. We also identified CYP with chronic comorbidities in two or
522 more body systems and with the following single diagnoses: asthma, diabetes, epilepsy, sickle cell
523 disease and trisomy 21. These single diagnoses were identified as common long-term conditions in
524 CYP and from single case studies, clinicians, patient groups and adult studies speculated to be at
525 increased risk from SARS-CoV-2.^{10,11}

526 Data availability statement

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

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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 data¹² 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 England¹⁶ 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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683 Author Contributions Statement

684 Study Design: CS, DO, RH, JW, ML, MC, DH, SL, ED, PD, SK, EW, KL, RV, LF.

685 Data collection and analysis: CS, DO, LF, KL

686 Data interpretation: CS, DO, EH, JW, ML, MC, DH, SL, ED, PD, SK, EW, KL, RV, LF. Reviewed underlying
687 data CS, DO, LF

688 First draft: CS

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690

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692 The authors declare no competing interests.
693

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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-incident 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.

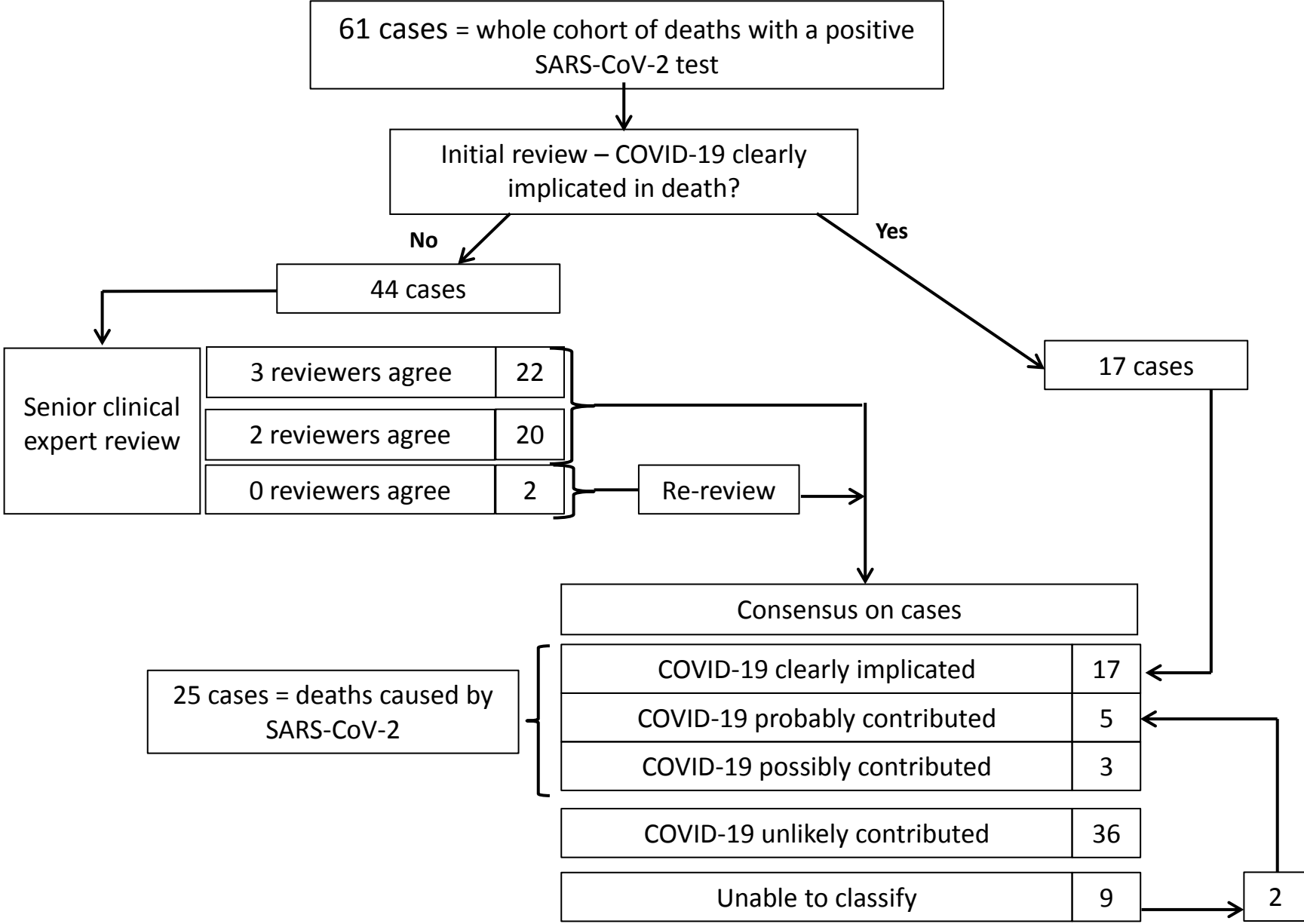
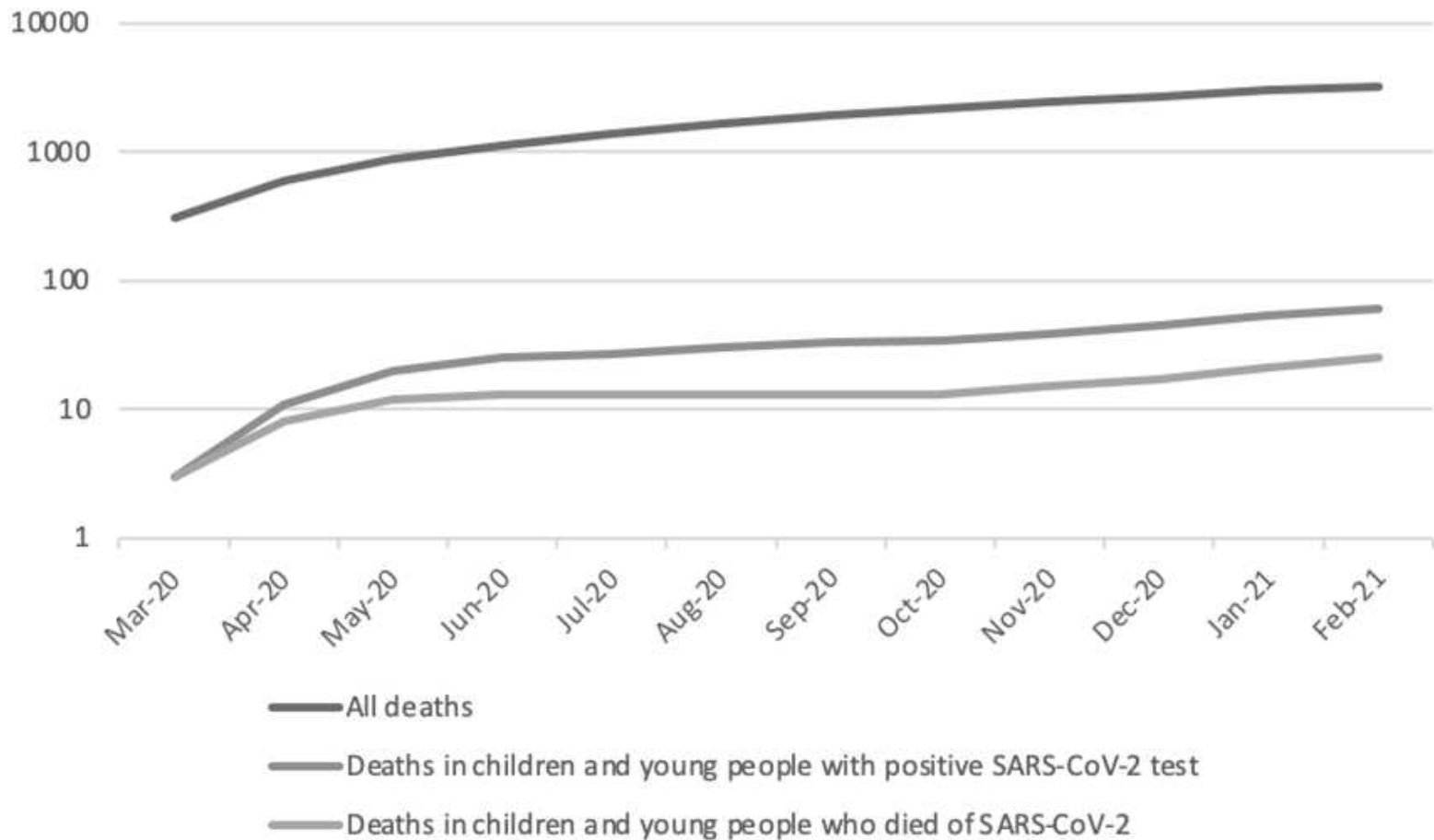
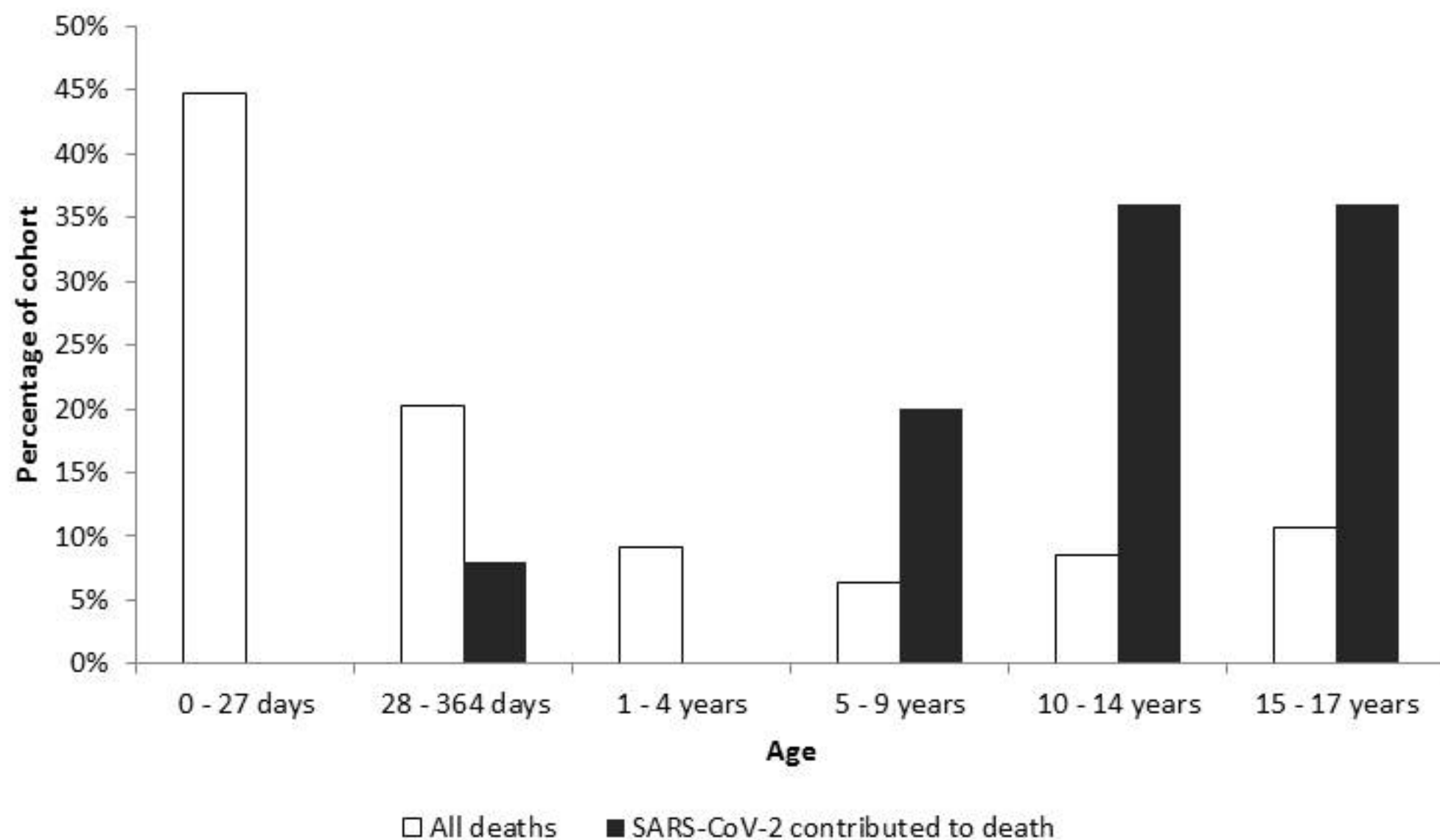


Figure 2 is a graph demonstrating the cumulative number of deaths for all Children and Young People (CYP) who died with a positive SARS-CoV-2 test in the study period (March 2020 to February 2021). It compares the number of CYP who died of SARS-CoV-2, the number of CYP who died with a positive SARS-CoV-2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



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 chart 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).

