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

3

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32 **Abstract**

33 Identifying which children and young people (CYP) are most vulnerable to serious SARS-CoV-
34 2 infection is important to guide protective interventions.

35

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

43

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

50

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

60

61

62

64 **Main Text**

65 **Introduction**

66

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

75

76 Early in the pandemic, guidance from the UK Royal College of Paediatrics and Child Health
77 (RCPCH) identified CYP with immunodeficiency or immunosuppression, and those with
78 certain malignancies, as having the greatest vulnerability to COVID-19.¹⁰ However, CYP with
79 a broad range of other conditions have also been highlighted as being potentially clinically
80 extremely vulnerable (CEV). CYP who are identified as CEV have been advised to take
81 additional “shielding” precautions to reduce the risk of SARS-CoV-2 infection in many
82 countries. These include measures that may result in harm to CYP and their families,
83 including those associated with reduced social mixing and restriction of in-person schooling.

84

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

92

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

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

104

105

106 **Results**

107 There were 1,242,197 emergency non-traumatic hospital admissions in England (hereafter
108 “admissions”) between 01 Feb 2019 and 31 Jan 2021 involving 892,906 CYP; 699,397 (78%)
109 had only one admission. During 2020-21, there were 470,606 admissions: 6,338 with COVID-
110 19 amongst 5,830 CYP; 712 with PIMS-TS amongst 690 CYP and 463,556 for other causes
111 amongst 367,637 CYP. In comparison, there were 771,591 admissions for 587,115 CYP
112 during 2019-20, of which 6968 were due to influenza in 6,780 CYP (see supplementary
113 material 1 table S1 and S15). 69.8% of CYP admitted due to PIMS-TS had no prior hospital
114 admissions, compared with 49.5-54.4% in all other cohorts.

115

116 The distribution of admissions by age, sex and ethnicity differed between the COVID-19,
117 PIMS-TS, and other cohorts (Table 1). A higher proportion of the PIMS-TS cohort was male
118 (63.5%) compared to the other cohorts (52.8-54%). Overall, 30.9% of admissions with
119 COVID-19 were in infants (children aged under 1 year, including neonates under 1 month of
120 age, and post neonatal infants aged 1-11 months), similar to other pandemic year
121 admissions and total admissions in 2019-20, but more than for influenza (17.1%) during this
122 time period. Amongst PIMS-TS, only 10.3% of admissions were in infants, whereas >85%
123 were among 1-14 year-olds. CYP with non-White ethnicity made up 41.9% of COVID-19
124 admissions, and 60.0% of PIMS-TS admissions, higher than the other hospitalization cohorts
125 we examined. There were more admissions in CYP from more deprived neighbourhoods
126 compared with least deprived in all cohorts, as assessed using Index of Multiple Deprivation
127 (IMD) quintile category. Further description of how IMD is determined is available in the
128 supplementary material.

129

130 Amongst COVID-19 admissions, 53.9% had a recorded comorbidity, and 18.0% had a life
131 limiting comorbidity, higher than for other pandemic year admissions, all admissions in
132 2019-20, and influenza admissions in 2019-20 (Supplementary Table S1). Patterns of
133 comorbidities amongst admissions with PIMS-TS were different to the other cohorts, with
134 68.3% having any comorbidity recorded, of which 20.6% were life-limiting. Due to the multi-
135 system nature of PIMS-TS, and of limitations in how data are recorded within SUS, many of
136 the comorbidities recorded could have been related to complications of the disease, rather
137 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.

170

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

179

180 *Comorbidities*

181 The odds of admission to PICU were increased amongst CYP with any comorbidity compared
182 with no comorbidity in all cohorts (supplementary material 2). The increases in odds of PICU
183 admission associated with having each of any comorbidity, a life-limiting comorbidity, or
184 comorbidities in more than one body system for COVID-19 (Figure 1), had overlapping
185 confidence intervals with those for all admissions in 2019-20 and influenza admissions in
186 2019-20, but were lower than for other pandemic year admissions. Odds ratios for PIMS-TS
187 admissions were consistently the lowest of any cohort for each comorbidity category,
188 although confidence intervals often overlapped.

189

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

201

202 Asthma, diabetes, epilepsy and trisomy 21 each increased risk of PICU admission for COVID-
203 19, although sickle cell disease did not (Figure 4). Increases in odds for COVID-19 appeared
204 broadly similar to those for other cohorts although confidence intervals were wide,
205 particularly for PIMS-TS.

206

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

215

216 **Discussion**

217

218 We found that very few CYP admitted to hospital in England due to COVID-19 or PIMS-TS
219 went on to develop severe disease or die. Of the 12.02 million 0-17 year olds in England
220 during 2020, 1 in 2062 (n= 5830) were admitted to hospital due to COVID-19, and 1 in
221 47,903 (n=251) were admitted to PICU. This represented only 1.3% of all secondary care
222 admissions in the pandemic year and less than 5% of non-traumatic emergency PICU
223 admissions. Eight of these CYP died within 28 days of admission to hospital. For PIMS-TS, 1
224 in 17,425 (n=690) of CYP in England were admitted to hospital, 1 in 38,911 (n=309) were
225 admitted to PICU, and fewer than 5 children died. This likely represents all PIMS-TS cases
226 nationally over the study period, as the vast majority will have required hospitalisation.

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

235 Of the 251 CYP admitted to PICU with COVID-19, 91% (n=229) had an underlying condition
236 or comorbidity. The odds of PICU admission due to COVID-19 were increased in all
237 comorbidity categories tested except sickle cell disease. We found that CYP with complex
238 medical problems across multiple body systems, and those with neurodisability, were at
239 greatest risk. This pattern is described in previous work,¹² and is consistent with our meta-
240 analysis of the published data, where each increase in number of pre-existing conditions
241 was associated with increased odds of PICU admission and death for COVID-19 [R.
242 Hardwood et. Al, unpublished¹³]. Increases in odds of PICU admission associated with
243 comorbidities in PIMS-TS were lower than for COVID-19, but are difficult to interpret; coding
244 of PIMS-TS admissions suggested two-thirds had a comorbidity, whilst three quarters had no
245 prior admissions to hospital. When codes which include known cardiac and haematological
246 complications of PIMS-TS were excluded, estimates for comorbidities in these admissions

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

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

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

271 When absolute risk was examined, the increases in risk associated with comorbidities were
272 relatively small in the COVID-19, other pandemic year, all admissions 2019-20 and influenza
273 cohorts, although greater for COVID-19 than other groups. For example, for the 229 CYP
274 with comorbidity in one body system admitted to PICU with COVID-19, the increase in risk
275 above those without comorbidities was 2% for COVID-19, 0.75% for all admissions in 2019-
276 20 and 1.3% for influenza. Combinations of comorbidities increased risk the most, although

277 again numbers were very small. Amongst the 414 admissions with respiratory and
278 neurological comorbidities, the increase in risks were 18.6% for COVID-19 compared with
279 12.3% for influenza and 7-8% for other cohorts. Whilst this greater increase in absolute risk
280 with COVID-19 appeared significant for body system comorbidities and their combinations,
281 confidence intervals overlapped for all specific conditions.

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

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

298 Strengths and Limitations

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

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

310 As the pandemic progresses and variants continue to emerge, the risks posed by SARS-CoV-
311 2 amongst CYP may change. Our data included children infected with the Alpha variant
312 (from November 2020 onwards) but did not include children infected with the Delta
313 (B.1.617.2) variant, dominant in the UK since May 2021. The Delta variant has higher
314 transmissibility, and prevalence, and there have been suggestions of greater severity in CYP,
315 although the evidence for this is mixed.²³ Further population-level analyses are needed to
316 explore the effect of this and other factors on disease severity in CYP as new data become
317 available.

318

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

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

337 incidental positive PCR tests. We used admission to PICU as an indicator for disease severity
338 and were not able to examine the level of intensive support needed whilst in critical care.
339 Our results may also have been affected by changes to thresholds for PICU admission, and
340 coding practices, as the pandemic progressed and in comparison to the previous years. Our
341 estimate for number of deaths due to COVID-19 and PIMS-TS only include hospitalised CYP,
342 and so will not include those who died at home or in an emergency department prior to
343 admission. Note that our linked study of all CYP deaths up to 28th Feb 2021 identified 25
344 deaths across all places of death, and provides a more complete analysis of mortality risk
345 associated with SARS-CoV-2.²⁴

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

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

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

370

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377 analysis.

378 Author contribution statement

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

382 Competing Interest Statement

383 The authors declare there are no competing interests

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394 Tables

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396
397

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)

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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)

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405 **Figure captions**

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

408
409 Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission
410 within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD
411 category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the right panel.
412 Observations: n=6338 COVID-19 admissions; n=710 PIMS-TS admissions; n= 463371 other pandemic year admissions; n=771357 all admissions 2019-20;
413 n=influenza admissions 2019-20. These results are available in full in supplementary material part 2.

414
415
416 **Figure 2** Odds ratios and percentage point difference in predicted probability with 95% confidence intervals for admission to PICU by body system
417 comorbidities within each cohort, adjusted for age, sex, IMD category, ethnicity

418
419 Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission
420 within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD
421 category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the middle panel.
422 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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424
425 **Figure 3** Odds ratios and predicted probability with 95% confidence intervals for admission to PICU by comorbidity combinations within each cohort, adjusted
426 for age, sex, IMD category, ethnicity

427
428 Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission
429 within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD
430 category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the middle panel.
431 Number of observations in each model is shown in the right panel. These results are available in full in supplementary material part 2.

432
433 **Figure 4** Odds ratios and predicted probability with 95% confidence intervals for admission to PICU by selected diagnoses within each cohort, adjusted for
434 age, sex, IMD category, ethnicity

435
436 Legend: Output from Generalised Estimation Equation models. Each mark and line represents odds ratios with 95% confidence intervals of PICU admission
437 within each admission cohort amongst admission with each comorbidity group compared to those without any comorbidity adjusted for age, sex, IMD

438 category and ethnicity. Percentage point difference in predicted probability of PICU admission with 95% confidence intervals are shown in the middle panel.
439 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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441

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518

519 **Methods**

520 Data

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

531

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

535

536 1) Paediatric Intensive Care Audit Network (PICANet) data containing all Paediatric Intensive
537 Care (PICU) admissions in England.

538 2) Death registrations provided by the Office for National Statistics (ONS).

539 3) National Child Mortality Database (NCMD), which collects preliminary notification data
540 within 48 hours of death of a CYP death in England and Wales

541 4) SARS-CoV-2 PCR-testing data provided by Public Health England (PHE).

542

543 **Outcomes and Exposures**

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

547

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

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

555

556 *Reason for admission*

557 We used primary and secondary diagnoses coded to International Classification of Diseases
558 10 (ICD 10) to define all hospital admissions between 1st Feb 2019 and 31st Jan 2021. We
559 excluded all traumatic admissions (where the primary cause of admission was an external
560 cause in ICD-10), and non-emergency admissions (i.e. elective or maternity/newborn) from
561 the analysis, and classified the remainder into five cohorts:

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

568

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

573

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

578

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

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

585

586 *Socio-demographic exposures*

587 Age was categorised as neonates (admission within 1 month of birth), post-natal infants
588 (admission between 1 – 11 months of birth), 1-4 years, 5-9 years, 10-14 years and 15-17
589 years. We defined ethnicity as: White, Mixed, Asian, Black, Other and unknown. We used
590 Index of Multiple Deprivation (IMD) 2019 quintile category (hereafter IMD category) to
591 define area level socioeconomic status of CYP. Further details of how IMD is defined are
592 available in supplementary material 1.

593

594 *Co-morbidities*

595 We used published literature and guidance on shielding to identify co-morbidities likely to
596 increase risk of severe SARS-CoV-2 disease.^{10,13} We identified CYP with chronic medical
597 conditions by body system, those with life-limiting conditions, and those with asthma,
598 diabetes, epilepsy, sickle cell disease and trisomy 21, using recognised ICD-10 code lists.^{27,28}

599 Note that admissions amongst CYP with specific conditions were also included in the
600 broader body system diagnostic categories. We then defined additional co-morbidity groups
601 to examine vulnerability associated with multiple medical problems. These were defined as:
602 comorbidities in more than one body system; comorbidities in both neurological and
603 respiratory, neurological and cardiovascular, or respiratory and cardiovascular body
604 systems. We compared admissions amongst CYP with each comorbidity category to CYP
605 with no comorbidities in any category in all analyses.

606

607 **Statistics and Reproducibility**

608 First we described the characteristics of each of the five cohorts: admissions due to COVID-
609 19, admissions due to PIMS-TS, other non-traumatic admissions in 2020/21 (hereafter
610 “other pandemic year admissions”), all non-traumatic admissions in 2019/20, and
611 admissions due to influenza in 2019/20. We suppressed cell counts with small numbers
612 (where $n < 5$) due to the risk of identification of individuals, in line with guidance from data
613 providers used in this study.

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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).

637 **Ethics approval and legal basis for data linkage and analyses**

638 Ethics approval was provided after review by Yorkshire and the Humber, South Yorkshire
639 NHS Research Ethics Committee on 10th June 2021 (Reference 21/YH/0127).

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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.

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

650

651 **NCMD**

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

663 **PICANet**

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

671

672 **Data availability Statement**

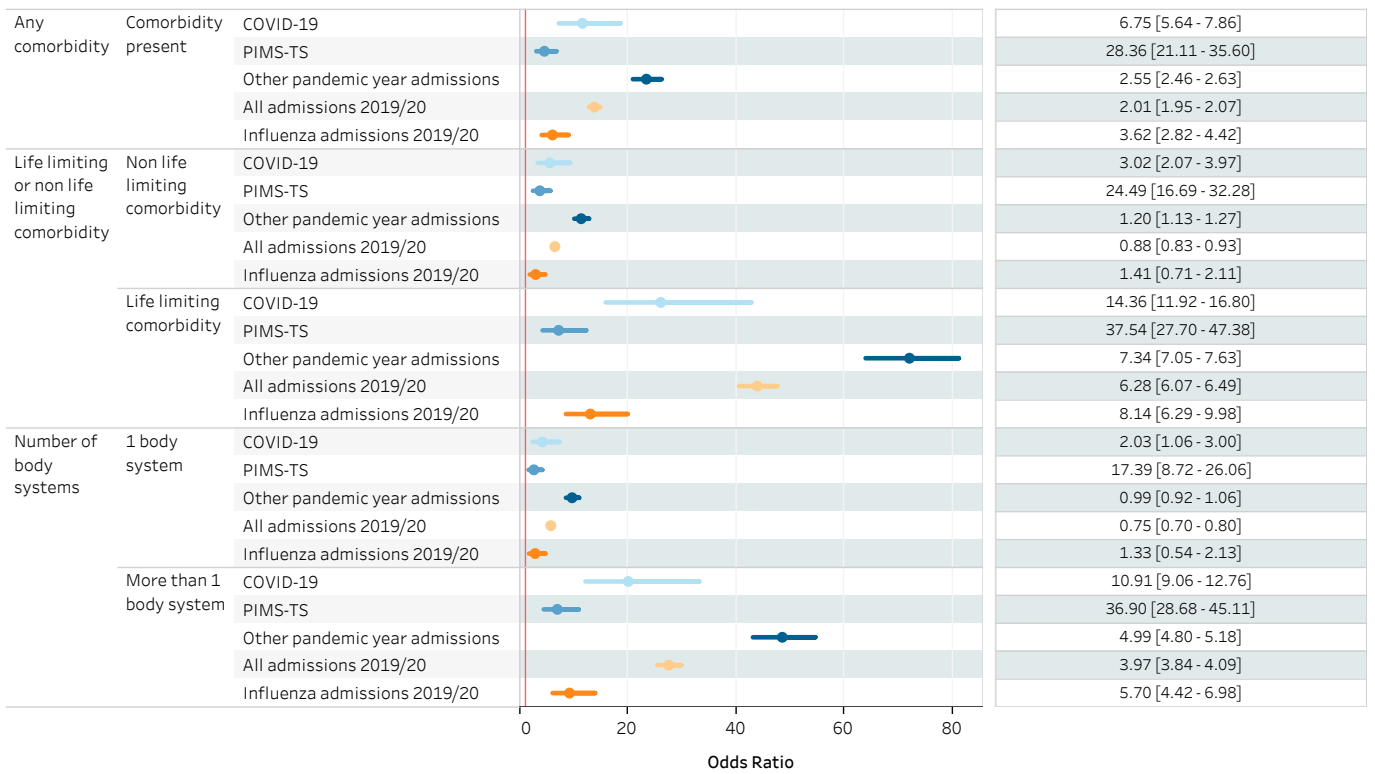
673

674 These analyses were undertaken using datasets held by NHS England for the use of ongoing
675 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 analyse 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

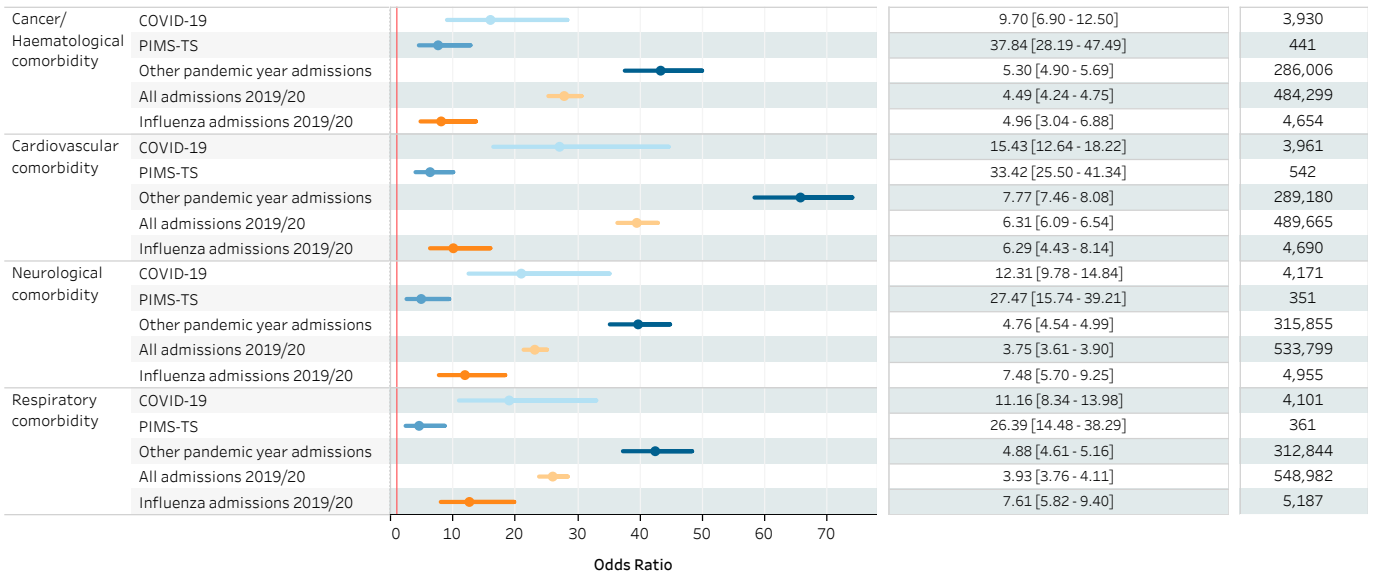
% difference in predicted probability



Odds ratios

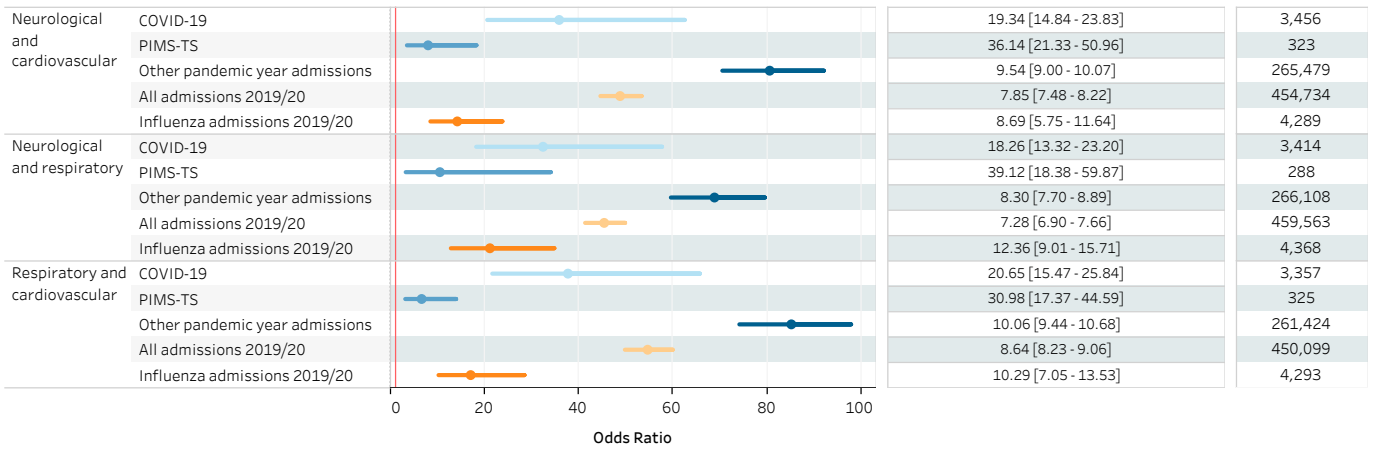
% difference in predicted probability

observations



Odds ratios

% difference in predicted probability observations



% difference in predicted probability
19.34 [14.84 - 23.83]
36.14 [21.33 - 50.96]
9.54 [9.00 - 10.07]
7.85 [7.48 - 8.22]
8.69 [5.75 - 11.64]
18.26 [13.32 - 23.20]
39.12 [18.38 - 59.87]
8.30 [7.70 - 8.89]
7.28 [6.90 - 7.66]
12.36 [9.01 - 15.71]
20.65 [15.47 - 25.84]
30.98 [17.37 - 44.59]
10.06 [9.44 - 10.68]
8.64 [8.23 - 9.06]
10.29 [7.05 - 13.53]

observations
3,456
323
265,479
454,734
4,289
3,414
288
266,108
459,563
4,368
3,357
325
261,424
450,099
4,293

Odds ratios

% difference in predicted probability observations

