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Characteristics of Severe Acute Respiratory Syndrome Coronavirus-2 Infection and Comparison With Influenza in Children Admitted to U.K. PICUs

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OBJECTIVES: Severe acute respiratory syndrome coronavirus-2 affects adults disproportionately more than children. A small proportion of children with severe acute respiratory syndrome coronavirus-2 required admission to a PICU. We describe the nationwide U.K. PICU experience of severe acute respiratory syndrome coronavirus-2 infection during the first wave of the pandemic and compare this with the critical care course of the 2019 influenza cohort.

DESIGN: Prospective nationwide cohort study of characteristics of severe acute respiratory syndrome coronavirus-2–positive children. Data collection utilized routine Pediatric Intensive Care Audit Network and severe acute respiratory syndrome coronavirus-2–specific data.

SETTING: All U.K. PICUs.

PATIENTS: Children less than 18 years old, admitted to U.K. PICUs between March 14, 2020, and June 13, 2020, and a positive severe acute respiratory syndrome coronavirus-2 polymerase chain reaction. Children admitted to U.K. PICUs in 2019 with influenza provided comparison.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We identified 76 PICU admissions among 73 children with a positive severe acute respiratory syndrome coronavirus-2 polymerase chain reaction test. Prevalence of PICU admissions per million was 5.2 for children versus 260 for adults. Ten children (14%) were identified on routine screening. Seventeen children (23%) had pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2. Seventeen (23%) had coinfections. Invasive ventilation was required in seven of 17 children (41%) with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2 versus 38 of 56 other severe acute respiratory syndrome coronavirus-2 positive children (68%), with 77% requiring vasoactive support versus 43%, respectively. Seven children (10%) died. In comparison with influenza children, severe acute respiratory syndrome coronavirus-2 children were older (median [interquartile range]: 10 [1–13] vs 3 yr [1–8 yr]), more often Black or Asian (52% v 18%), higher weight *z* score (0.29 [–0.80 to 1.62] vs –0.41 [–1.37 to 0.63]), and higher deprivation index (3.3 [–1 to 6.3] vs 1.2 [–1.8 to 4.4]). Comorbidities, frequency of organ supports, and length of stay were similar.

CONCLUSIONS: This nationwide study confirms that PICU admissions with severe acute respiratory syndrome coronavirus-2 infections were

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infrequent. We have reported similarities and differences in sociodemographic characteristics, organ support interventions, and outcomes of children affected by severe acute respiratory syndrome coronavirus-2 compared with influenza.

KEY WORDS: coronavirus disease 2019; epidemiology; influenza; intensive care units; pediatric; severe acute respiratory syndrome coronavirus-2

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, the cause of coronavirus disease (COVID-19), appears to be infrequent and less severe in children than in adults(1–4). Despite the apparent lower risk, some children with SARS-CoV-2 infection have required admission to PICUs with associated morbidity and mortality(5–8). SARS-CoV-2 infection has also been implicated in a multisystem inflammatory illness in children, commonly referred to as either pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C) (9, 10). To date, however, there have been few multicenter publications describing children severely affected by SARS-CoV-2, and none that represent a whole national population.

The aim of this study was to describe the clinical characteristics, management, and outcomes for children with confirmed SARS-CoV-2 infection prior to or during admission to a PICU in the United Kingdom during the first wave of the pandemic, using the Pediatric Intensive Care Audit Network (PICANet) national dataset. Influenza infections are associated with significant morbidity and mortality in children of all ages. As another respiratory infection with varying severity of illness with potential systemic complications, influenza may have several similarities with COVID-19, including hospitalization rates (11). However, there is no literature comparing the critical care course of the two illnesses in children. The study compares the SARS-CoV-2 cohort with a historical cohort of children admitted to PICU with influenza. Additionally, demographic and clinical characteristics for SARS-CoV-2–positive children with a clinical phenotype of PIMS-TS are compared with those who did not have PIMS-TS. This information will inform the ongoing management of these children and provide guidance for health professionals and families.

METHODS

Inclusion Criteria

This nationwide prospective observational study included children less than 18 years old who were admitted to one of the 24 U.K. PICUs and belonged to either 1) the SARS-CoV-2 cohort: a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test any time during or immediately prior to the admission episode during the 3-month period between March 14, 2020 and June 13, 2020 or 2) the influenza cohort: a primary diagnosis of influenza admitted to a U.K. PICU between January 1, and December 31, 2019. The SARS-CoV-2 cohort included any child with a positive RT-PCR test regardless of indication for testing, symptomatology, or presentation such as asymptomatic, respiratory failure, or PIMS-TS/MIS-C.

Data Collection

PICANet collects, analyses, and reports on information related to all admissions from all U.K. PICUs (12). PICANet has a validated online data entry system, and data quality is audited to ensure highest quality data. The core PICANet dataset includes information related to patient demographics, diagnoses, interventions included in the pediatric critical care minimum dataset, and outcome at discharge from PICU, as well as severity of illness variables for calculation of the Pediatric Index of Mortality (PIM) 3 score (13).

Data collection was expanded during the SARS-CoV-2 pandemic to include additional information concerning all children who tested positive for SARS-CoV-2 either prior to or during the PICU admission (**Supplemental Digital Content 2**, http://links.lww.com/CCX/A533 and **Supplemental Digital Content 3**, http://links.lww.com/CCX/A534). This included the following: SARS-CoV-2 status at admission, up to three rounds of testing including date and time of testing, reason for testing (suspected infection or routine testing), types of sample taken, results of each test, laboratory markers at admission, coinfections, symptoms, and medications. An admission episode was defined as any continuous period of intensive care, including direct transfers between PICUs. Similarly, children

readmitted to a PICU within 48 hours of index discharge were considered as having one continuous admission event. Townsend deprivation index scores were allocated to children by postcode of residence (14). Comorbidities were reviewed for all children and grouped into major diagnostic categories. SARS-CoV-2 positive children were categorized by PICU clinicians as to whether they presented with PIMS-TS or not. The SARS-CoV-2 specific dataset was set up prior to publication of case-definitions for MIS-C published by either the U.S. Centers for Disease Control and Prevention or the World Health Organization (15, 16).

Data were validated with all PICUs to ensure 100% case-ascertainment of all SARS-CoV-2 positive patients in the United Kingdom. Any missing data items were requested from units to ensure completeness of the data.

Statistical Analysis

Descriptive data were reported as numbers and percentages for categorical variables and medians with interquartile ranges (IQRs) and mean and SDs for continuous variables. *z* scores of weight-for-age were calculated to compare the weight of a child with the mean weight for a child of the same sex and age using the U.K. World Health Organization Growth References, accounting for preterm birth where required(17, 18). Estimates and 95% CIs for the difference between the SARS-CoV-2 and influenza cohorts were obtained using *t* tests for continuous data and two-sample test of proportions for discrete variables. SARS-CoV-2 incidence rates were calculated per 1,000,000 population using 2019 midyear population estimates from the Office for National Statistics (19). Comparable rate of ICU admission for adults was calculated using the intensive care national audit and research centre case-mix program COVID-19 report dated 12 June 2020 and midyear population estimates for United Kingdom, Wales, and Northern Ireland from the same Office for National Statistics report (20). All data were analyzed using STATA 16.0 (College Station, TX).

Ethics and Research Governance Approvals

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

RESULTS

During the study period, 73 children with a positive SARS-CoV-2 polymerase chain reaction (PCR) had 76 PICU admission episodes. Sixty nine children (95%) were admitted to a PICU in United Kingdom. During the same period in United Kingdom, 1,008 children were admitted to hospital with a positive SARS-CoV-2 PCR, with PICU admission rate of 6.85% (21). Eighteen of the 24 U.K. PICUs had at least one child admitted with SARS-CoV-2. The population incidence of children with SARS-CoV-2 requiring PICU was 5.2 per million U.K. children 0–17 years old during the study period, compared with 260 per million adults requiring intensive care admission in a comparable time period.

Figure 1 shows weekly numbers of newly confirmed SARS-CoV-2 infections and associated cumulative totals among children admitted to PICU during the study period. The peak was in week 17 (20–26 April 2020) with 10 children testing SARS-CoV-2 positive. Over half of these children (n = 39; 53%) were admitted to PICUs in London with a further two fifths (n = 30; 41%) admitted to PICUs in the rest of United Kingdom, and very few children admitted to PICUs in the devolved U.K. nations (n = 4; 6%).

Characteristics of SARS-CoV-2–Positive Children and Comparison With Influenza Cohort

The characteristics of the SARS-CoV-2–positive children admitted to PICUs during the study period are presented in **Supplementary Digital Content 1** (http://links.lww.com/CCX/A532) and are compared with the 2019 cohort of 243 children admitted to PICU with influenza.

In comparison with influenza children, SARS-CoV-2 children were older (median [IQR]: 10 [1–13] vs 3 yr [1–8 yr]). Children under 6 years comprised only one third of the SARS-CoV-2 cohort (33%) compared with almost two thirds of the influenza cohort (63%). The two cohorts were similar in terms of sex,

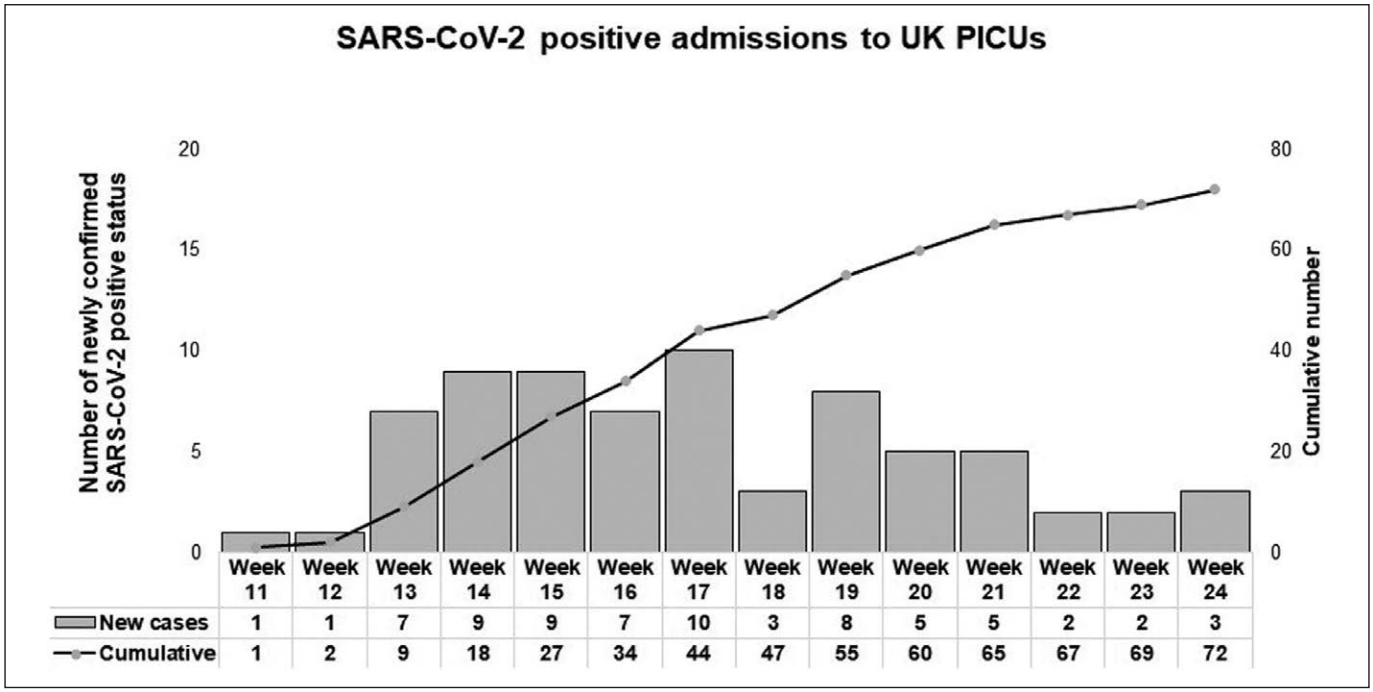

Figure 1. New and cumulative confirmed cases of coronavirus disease 2019 in children treated in PICU in the United Kingdom, by date of first laboratory confirmation. Please note information on one children excluded from this graph as date first confirmed positive not known. SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

proportion of unplanned admissions, and PIM3 predicted mortality risk. Children in PICU with SARS-CoV-2 were from more deprived areas than the influenza cohort (mean [SD] of Townsend index of deprivation: 2.7 [4.05] vs 1.5 [3.75]; mean difference: 1.21 [0.20–2.22]). In addition, there was a suggestion of higher proportions of children of Black and Asian ethnicity (n = 38; 52%) in the SARS-CoV-2 group compared with the influenza (n = 43; 18%) cohort, although one fifth of the influenza cohort had missing ethnicity data. The proportion of children with underlying comorbidities appeared similar between children with SARS-CoV-2 (31; 43%) and influenza (121; 50%). The most common comorbidity for both groups of children were similar, with neurologic/developmental (SARS-CoV-2: 25%; influenza: 24%) and prematurity (SARS-CoV-2: 11%; influenza: 12%) being the most common. A higher proportion of children with chronic pulmonary diseases were observed in the influenza cohort compared with the SARS-CoV-2 cohort. However, the numbers of children affected in either group were small. Only eight children (11%) with SARS-CoV-2 infection met the Public Health England (PHE) criteria for the extremely vulnerable category requiring shielding (22). Differences in distribution of weight z scores suggested that the SARS-CoV-2 cohort were heavier than the influenza cohort (0.29 [–0.80 to 1.62] vs –0.41 [–1.37 to 0.63]). Again, there were high levels of missing data in the influenza cohort.

SARS-CoV-2 Symptoms and RT-PCR Tests

Details of the symptoms and testing for the SARS-CoV-2 cohort are summarized in Supplemental Digital Content 2 (http://links.lww.com/CCX/A533). Of the common symptoms, 63% of the SARS-CoV-2 cohort reported fever (> 37.8°C), 31·5% cough, and none were reported to have anosmia. Other commonly reported symptoms were abdominal pain (26%), diarrhea (25%), rash (21%), and shock (21%). Nine children (12%) reported no symptoms.

A positive SARS-CoV-2 result was most commonly obtained between 24 hours prior to (n = 17) and 48 hours post PICU admission (n = 34). Most children were tested for SARS-CoV-2 due to a suspected infection (n = 58; 79%). However, 10 (14%) were detected during routine screening. Details on SARS-CoV-2 testing were unavailable for five children; 176 test results from 68 children were available for analysis. A range of samples were tested including nasopharyngeal aspirate (n = 109; 56% positive), throat swab (n = 68; 59% positive), endotracheal

secretions (n = 26; 42% positive), and bronchoalveolar lavage (n = 17; 41% positive). Testing types were not mutually exclusive between testing episodes, and a child may have had more than one type of test in a testing session; however, the majority of children had one single test reported to PICANet (n = 53; 78%).

Seventeen children (23%) had other coinfections recorded (Supplemental Digital Content 2, http://links.lww.com/CCX/A533). This included other viral infections in 13 children, bacterial in seven children, and fungal in four children, with multiple infection types reported in some (n = 5; 7%).

Management and Outcomes for SARS-CoV-2–Positive Children and Comparison With Influenza Cohort

A range of interventions were reported in SARS-CoV-2–positive children (Supplemental Digital Content 3, http://links.lww.com/CCX/A534); although given their comorbidities, it is not possible to attribute the interventions to SARS-CoV-2 given multiple comorbid conditions, alternative diagnoses, and coinfections. Antiviral medications were only reported in 11 children (15%) in the SARS-CoV-2 cohort, with remdesivir (n = 8/11; 73%) being the most common. Twenty-two children (30%) received immunomodulatory/anti-inflammatory medications including IV immunoglobulin (n = 14; 19%), azithromycin (n = 14; 19%), and dexamethasone (n = 6; 8%). Of note, 54 children (74%) received antibiotics during their PICU stay, but only five children (6%) had a confirmed bacterial coinfection.

A lower proportion of children with SARS-CoV-2 (n = 45; 62%) received invasive ventilatory support compared with 75% of children with influenza. However, a higher proportion of children required vasoactive interventions in the SARS-CoV-2 cohort (51%) compared with the influenza cohort (35%). Some of these differences may, however, be related to the subgroup of children with a PIMS-TS phenotype (Supplemental Digital Content 3, http://links.lww.com/CCX/A534). The non–PIMS-TS subgroup of the SARS-CoV-2 cohort did have a comparable proportion of children requiring invasive mechanical ventilation (68%) and vasoactive support (43%) relative to the influenza cohort. Very small numbers of children in both the SARS-CoV-2 and influenza cohorts received high frequency oscillation, inhaled nitric oxide, renal replacement therapy, and extracorporeal membrane oxygenation. The duration of respiratory, vasoactive supports, as well as PICU length of stay, was similar between the two groups.

Seven children in the SARS-CoV-2 cohort died while on PICU, although two deaths occurred more than 28 days after the first recorded positive SARS-CoV-2 test. Two of the seven deaths occurred in children admitted to PICU for other unrelated critical illness, with SARS-CoV-2 infection only identified on screening during their PICU stay. Their deaths may have been unrelated to COVID-19 illness. All other deaths potentially associated with COVID-19 illness occurred in children 12 years old or older. In addition, four of the seven children had other recorded coinfections. Five of the seven children, including three of the five with potentially COVID-19 associated deaths, had other significant comorbidities or other significant noninfective diagnoses. All seven children received invasive ventilation (median length of ventilation = 8 d [3–35 d]), and four children also received vasoactive support prior to death.

Characteristics of Children With PIMS-TS and Positive SARS-CoV-2 PCR

Supplemental Digital Content 3 (http://links.lww.com/CCX/A534) compares the characteristics of the SARS-CoV-2 positive children presenting with PIMS-TS phenotype (n = 17; 23%) compared with the rest of the cohort (n = 56; 77%). In comparison with non PIMS-TS children, the PIMS-TS subgroup of children were broadly similar in terms of their ethnicity, sex, but more likely to be admitted to a London PICU, older age-group, heavier, and from a less deprived area. The majority of the PIMS-TS cohort had no underlying comorbidities (n = 12; 71%) compared with others (n = 25; 45%). The PIMS-TS subgroup needed respiratory support less frequently (59% vs 71%) but required vasoactive support more frequently (77% vs 43%) than the children without PIMS-TS. Similarly, children with PIMS-TS were more likely to receive IV immunoglobulin, whereas small numbers in each group were treated with dexamethasone. There was only one death reported in the PIMS-TS subgroup.

DISCUSSION

Using the PICANet dataset, we have described, at a population level, the low incidence of need for an

intensive care admission in children (5.2 per million children) compared with adults (260 per million adults). We have also shown that only a small proportion of children hospitalized with SARS-CoV-2 required PICU (6.85% in United Kingdom). PICU admissions were highest in London with noticeable and obvious geographical variation across the different U.K. regions. We showed clear differences in age range as well as other demographic characteristics known to be associated with increased severity of risk of SARS-CoV-2: weight z scores, ethnicity, and deprivation indices, as well as the requirement for organ support between SARS-CoV-2 and influenza (2, 5). Importantly, a small but significant proportion of children were identified to have SARS-CoV-2 infection on routine screening of asymptomatic patients admitted to PICU for other reasons. This suggests that routine screening may need to be implemented regularly, especially as some children tested positive more than 1 week after admission, indicating possible nosocomial infection. Coinfections were recorded in 15% of SARS-CoV-2 cases. We also note that in the SARS-CoV-2 cohort, coinfection with other pathogens was relatively low and that although many children were treated with antibiotics, few had bacterial infections detected. Over 90% of children were discharged alive after a relatively short PICU length of stay, regardless of presentation with a respiratory or a PIMS-TS phenotype despite a high proportion of children admitted with significant comorbidities and other primary diagnoses. Two of the deaths were also reported greater than 4 weeks after diagnosis of SARS-CoV-2 infection. Of note, the U.K. government reports only those deaths within 4 weeks of a diagnosis of SARS-CoV-2 infection as COVID-19 associated (23).

The peak in PICU admissions occurred in the week commencing April 1, some weeks after the peak in adult ICU admissions (24), possibly related to the increase in PICU admissions of patients with PIMS-TS (9). This report is limited to the subgroup of PIMS-TS who were SARS-CoV-2 PCR positive. Given the far higher numbers of patients with PIMS-TS who were SARS-CoV-2 PCR negative (9, 25), the population incidence of PICU admission, as well as the geographical and temporal distribution, may be slightly different when all patients with PIMS-TS are considered. It is unclear whether there are differences between the PCR-positive and PCR-negative PIMS-TS children either in etiopathogenesis or in clinical presentation. Among the PIM-TS patients in our cohort, we noted that 11 of 17 (65%) received IV immunoglobulin as part of their treatment, in line with the latest U.K. Delphi recommendations (26). We have shown a significantly higher incidence of SARS-CoV-2 infection among patients of Black and Asian ethnicity (52%), perhaps even more so than children with all levels of severity of SARS-CoV-2 infection (22%) reported by the International Severe Acute Respiratory and Emerging Infection Consortium study (4), and in adults requiring ICU admission (25%) for COVID-19 in the United Kingdom in the same time period (27). In keeping with other reports from U.K. adult ICUs (27), children from areas of higher deprivation were overrepresented in this cohort when compared with other respiratory viral illness such as influenza. However, in part, these effects may also reflect the particular geography of infection and childhood population, with London much more severely affected than other parts of the United Kingdom, which are less deprived and less ethnically diverse (28). Association between ethnicity and outcomes has been previously reported by PICANet with a risk-adjusted odds ratio for mortality for south Asian children admitted to PICU of 1.36 overall, rising to 2.4 in the least deprived fifth of the population (29). Exact reasons for higher risk of severe infection in the Black and Asian ethnicities are unclear.

Compared with the influenza cohort, SARS-CoV-2 appeared to have a lower proportion of children with chronic pulmonary diseases, consistent with the only other study comparing the two infections in children (11). Children with chronic pulmonary diseases were considered to be at high-risk of severe COVID-19, as were children with significant immunodeficiency, malignancy, and other rare diseases. This group of children and adults was provided with "shielding" guidance from PHE (22). Although it is encouraging that there was a low requirement of PICU admission overall, and no significant overrepresentation in any of these risk groups, it remains unclear whether this was a result of the "shielding" guidance. Coinfection with other viral pathogens in this study was uncommon, which has implications for isolation practices and personal protective equipment policies. However, since the reported period of the pandemic occurred in spring, lower rates of viral transmission might be expected. Rates of coinfections with other respiratory viruses

may be substantially higher in the winter period. Of note, information about the site or significance of the coinfection was unavailable and screening practices to detect coinfection may have varied between sites.

In a study of critically ill children with SARS-CoV-2 from 183 North American PICUs, 530 PICU admissions were reported, of whom 401 were children less than 18 years old (6). Similar to our report, they also observed relative sparing of infants and young children. The median age of SARS-CoV-2 positive children admitted to PICU of 10 years in this study was also consistent with other North American studies (5, 30). Likewise, the proportion of patients with preexisting comorbidities in this study was 43%, well within the wide range of 24–83% reported in different studies of children admitted to PICU (5–8, 30). The proportion of children requiring invasive mechanical ventilation (62%) was significantly higher than that reported in other PICU-based studies, ranging from 28% to 47% (5, 6, 8, 30). Direct comparisons are often difficult, given different PICU admission criteria, different thresholds for intubation between different centers and countries, the lack of comparable risk-stratification scores such as PIM3, and differences in the proportion of patients with PIMS-TS phenotype. It might suggest a lower threshold to intubate children in the United Kingdom, given the hypothetical concerns of high-flow nasal cannula oxygen and noninvasive ventilation being aerosol generating. However, given the duration of respiratory support and PICU length of stay being comparable not only to children with influenza in the same U.K. PICUs but also with other published SARS-CoV-2 PICU reports (5, 6, 8), this seems unlikely.

The major strength of this study is that we were able to report population-level incidence of PICU admissions with 100% case-ascertainment for the United Kingdom using PICANet, a well-established and high-quality database (12). This study was prioritized as an urgent public health study in the United Kingdom, which ensured rapid engagement by all PICUs, despite difficulties associated with restrictions associated with the COVID-19 pandemic. In addition, we were able to describe characteristics of SARS-CoV-2 infection in comparison with influenza admissions in children as well as the specific characteristics of the PIMS-TS subgroup of patients.

Despite the high-quality dataset, we were unable to ascertain the significance of the role SARS-CoV-2 infection played in either the PICU course or the outcomes of these children. It is possible that at least in some instances, SARS-CoV-2 infection may have had a relatively minor role, given that 14% were identified on routine screening, and 43% had significant preexisting comorbidities. Missing ethnicity data in the influenza cohort meant that we are uncertain about the increased susceptibility of serious SARS-CoV-2 infection in children of Black and Asian ethnic groups. We did not independently confirm the case-definitions of patients reported to have PIMS-TS within the dataset but relied on individual clinicians to do so. Children with PIMS-TS who tested PCR negative were not included in this report. Our customized dataset was limited to two other tests in addition to the first positive SARS-CoV-2 test. Some patients may have had more tests than reported in this study. The criteria for testing patients is likely to have differed between units, as well as with time within the same units due to increased access to testing in the latter half of the study period. A very small number of 16–17 years olds may have been admitted to adult ICUs rather than PICUs, and therefore, the population incidence rates may be a slight underestimate. This study is limited to information collected during the first wave of the pandemic in the United Kingdom, before the emergence of variant strains with potentially different characteristics.

Using the first nationwide PICU dataset, we confirm the very low incidence of serious SARS-CoV-2 infection in children in the United Kingdom. We have characterized the demographic factors, comorbidities, PICU interventions and have described the differences between this group and those admitted to PICU with influenza. We have also identified the detection of SARS-CoV-2 in critically ill children, in terms of testing time and type, plus the risk of coinfection. It is anticipated that this information is helpful for planning service provision, targeted public health measures, provide information of clinicians at the bedside to manage, and counsel families of critically ill children with SARS-CoV-2 infection.

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