Research Letter

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Incidence and severity of SARS-CoV-2 infection in children and young people with HIV in Europe

The European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) study group*

We assessed incidence of SARS-CoV-2 infection and disease severity among children and young people with HIV from cohorts across nine European countries. Of 1717 included, with median duration of follow-up 20.1 months, 134 (8%) had documented SARS-CoV-2 infection, a rate of 49 [95% confidence interval (CI) 42–58] per 1000 person-years. All symptomatic cases had mild coronavirus disease 2019 (COVID-19), three were hospitalized, and no deaths were reported, which may be reassuring for clinicians and families.

In adult studies HIV infection has been independently associated with poorer outcomes of coronavirus disease 2019 (COVID-19) [1–3]; however, there remains limited data in children and young people with HIV (CYPHIV).

We estimate the incidence of SARS-CoV-2 infection in CYPHIV in the European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) and describe the clinical characteristics of those with COVID-19.

EPPICC collects data on CYPHIV in routine care [4]. CYPHIV are followed from entry to HIV care to last visit in paediatric care, or in some cohorts through adult care. CYPHIV from 11 cohorts in 9 European countries who were diagnosed with HIV aged <18 years and in follow-up aged<25 years on/after 1 January 2020 (proxy for start of pandemic in Europe) were included.

SARS-CoV-2 infection was defined as documented positive PCR test based on clinical notes or linkage with national/regional SARS-CoV-2 databases. Multisystem Inflammatory Syndrome in Children (MIS-C) cases (WHO/ISARIC case definition [5]) were requested, but none identified.

Pseudonymized individual-level data were pooled using a modified HIV Cohorts Data Exchange Protocol (www.hicdep.org) and a standardized case report form based on WHO/ISARIC forms [5] to collect additional data on those with SARS-CoV-2 infection. All cohorts received local ethics approval where required.

Individuals were considered at risk from latest of 1 January 2020, and date of birth for those with vertically-acquired HIV or date first seen in HIV care for those with other modes of acquisition. Follow-up was censored at SARS-CoV-2 diagnosis, death, age 25 years or last visit before data cut-off.

Among those in HIV care at start of 2020, characteristics on 1 January 2020 were compared between those with and without SARS-CoV-2 infection, using chi-squared tests for categorical and Wilcoxon's rank-sum tests for continuous variables. COVID-19 severity was classified using WHO criteria [6].

Among 1717 CYPHIV included, the median [interquartile range (IQR)] duration of follow-up was 20.1 months (14.1–24.6), and median age on 1 January 2020 was 13.9 (9.1–17.8) years. One hundred and thirty-four (8%) were diagnosed with SARS-CoV-2 infection, an incidence rate of 49 (95% confidence interval 42–58) per 1000 person-years.

Among the 1688 CYPHIV in follow-up on 1 January 2020, those with SARS-CoV-2 infection were older than those without, had been diagnosed with HIV for a longer time, and were less likely to have an HIV RNA viral load<50 copies/ml (all $P < 0.06$), with no difference in CD4 count, antiretroviral treatment (ART) status or obesity (all $P > 0.35$). Of the 134 with SARS-CoV-2, 63 (47%) had known date of diagnosis: median age at diagnosis was 17.0 years, at which point 57/63 (90%) were on ART (Table 1).

Among 44/134 (33%) SARS-CoV-2 cases with clinical data available, 42 had symptom information, of whom 25 (60%) experienced ≥1 symptom of COVID-19. The most common symptoms were cough (13/42, 31%), fever (11/42, 26%), and anosmia and/or ageusia (11/42, 26%). COVID-19 was asymptomatic for 17 (39%), mild for 22 (50%) and unknown for 5 (11%); none had moderate, severe or critical disease.

Three individuals were hospitalized following SARS-CoV-2 diagnosis. The first was aged <10 years, recently diagnosed with HIV/AIDS, severely immunocompromised ($CD4^+$ 6 cells/mm^3) and had been on ART for

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Table 1. Demographic and HIV-related clinical characteristics of participants by SARS-CoV-2 infection status.

	SARS-CoV-2 infection ($N=134$)	No SARS-CoV-2 infection ($N=1583$)	*P*
	n (%) or median (IQR)		
Demographics			
Female sex	79 (59%)	871 (55%)	0.379
Ethnicity ($n=133$; 1570)			0.439
White	97 (73%)	1063 (68%)	
Black	29 (22%)	420 (27%)	
Other	7 (5%)	87 (6%)	
Vertically acquired HIV ($n=113$; 1367)	101 (89%)	1272 (93%)	0.148
Country			<0.001
Belgium	1 (1%)	58 (4%)	
Greece	0	21 (1%)	
Poland	1 (1%)	44 (3%)	
Portugal	1 (1%)	23 (1%)	
Romania	0	54 (3%)	
Russia	84 (65%)	841 (53%)	
Spain	23 (17%)	159 (10%)	
Sweden	0	113 (7%)	
UK	24 (19%)	270 (17%)	
Characteristics on 1 January 2020 ($n=130$ with SARS-CoV-2 infection and $n=1558$ without)[a]			
Age, years	15.8 (11.7, 18.8)	13.7 (8.9, 17.7)	0.002
Years since HIV diagnosis ($n=126$; 1483)	10.9 (4.8, 15.1)	9.1 (4.6, 13.2)	0.050
$CD4^+$ cell count in those ≥5 years ($n=109$; 1276)	713 (537, 916)	730 (531, 980)	0.456
$CD4^+$% in those <5 years ($n=7$; 144)	39 (30, 44)	37 (32, 44)	0.953
WHO advanced/severe immunosuppression for age[b] ($n=116$; 1420)	9 (8%)	119 (8%)	0.816
HIV viral load <50 copies/ml ($n=93$; 1240)	45 (48%)	726 (59%)	0.056
ART status			0.835
ART naïve	6 (5%)	79 (5%)	
Off ART (>7 days)	7 (5%)	102 (7%)	
On ART	116 (89%)	1353 (87%)	
Unknown	1 (1%)	24 (2%)	
Obesity[c] in those ≥2 years ($n=77$; 1035)			0.350
Underweight/normal weight	59 (78%)	856 (83%)	
Overweight	14 (18%)	131 (13%)	
Obese	3 (4%)	48 (5%)	
Characteristics at SARS-CoV-2 infection ($n=63$ with date of infection known)			
Age, years	17.0 (14.1, 19.5)	–	–
ART status		–	–
ART naïve	1 (2%)	–	–
Off ART (>7 days)	4 (6%)	–	–
On ART	57 (90%)	–	–
Unknown	1 (2%)	–	–
$CD4^+$ count in those ≥5 years ($n=48$)	721 (585, 973)	–	–
$CD4^+$% in those <5 years ($n=3$)	34 (33, 54)	–	–
HIV viral load <50 copies/ml ($n=50$)	39 (78%)	–	–
Reason for PCR test		–	–
Contact tracing	16 (25%)	–	–
Presented symptomatically	11 (17%)	–	–
Routine screening	2 (3%)	–	–
Unknown	34 (54%)	–	–
Any symptoms experienced (among those with clinical data ($n=42$)	25 (60%)	–	–
Cough	13 (31%)	–	–
Anosmia and/or aguesia	11 (26%)	–	–
Fever	11 (26%)	–	–
Headache	8 (19%)	–	–
Fatigue	7 (17%)	–	–
Runny nose	7 (17%)	–	–
Sore throat	7 (17%)	–	–

Only symptoms experienced by ≥10% of patients are listed in the table. Symptoms experienced by <10% of patients were: myalgia, vomiting, abdominal pain, diarrhoea, increased respiratory rate, joint pain, rash and wheezing. The '*n*' given refers to the number with nonmissing data, with data being complete if not specified.

[a]Excludes 4/134 diagnosed with COVID and 25/1583 not diagnosed with SARS-CoV-2 infection who were born or entered care >1 January 2020.

[b]WHO advanced/severe immunosuppression for age defined as $CD4^+$ lymphocyte percentage ($CD4^+$%) <30% for children <1 year of age, <25% for children aged 1–3 years, <20% for children aged 3–5 years, and <650 cells/mm^3 or <15% for children aged ≥5 years.

[c]Based on WHO BMI-for-age *z*-score: overweight corresponds to *z*-score ≥2, obese corresponds to *z*-score ≥3 [11,12].

<1 month. They were admitted for 23 days. Their symptoms included increased respiratory rate and wheezing. Chest X-ray was normal. They received oral fluids, interferon-alpha, ceftriaxone and ibuprofen; however, the primary reason for admission was not COVID-19. The second and third patients were older adolescents hospitalized for 1 and 3 days, respectively. Both had an HIV RNA viral load<50 copies/ml, were not significantly immunocompromised ($CD4^+$ >350 cells/mm^3), and had mild COVID-19.

Among the 44 patients with clinical data, 1 (3%) had ongoing symptoms at 6 months; they were not hospitalized, and their main ongoing symptom was fatigue. No deaths were reported.

This study represents the first multicountry description of SARS-CoV-2 infection and COVID-19 specifically among CYPHIV.

The incidence of diagnosed SARS-CoV-2 infection was relatively low, although the timeframe over which data were available varied by country, and in some cohorts only captured the early part of the pandemic. In the general population incidence of symptomatic COVID-19 among those <18 years across 10 European countries between August 2020 and September 2021 was estimated at 27 per 1000 population, lower than reported here [7]; however, comparison is difficult, given differences in setting, time period and case definition. Infection was more common among those who were older and those not virally-suppressed. An increased risk of infection with age is consistent with data from the general population [8].

Although this study includes relatively small numbers with SARS-CoV-2, there was no suggestion of increased risk of severe outcomes as observed in adult HIV populations, with none having WHO moderate/severe disease, few hospitalized and no deaths. A study from South Africa reported a two-fold increase in COVID-19 death among people aged ≥20 years with HIV compared to those without [1], although they were unable to adjust for key confounders such as comorbidities. The largest published study on people with HIV with COVID-19 is from the WHO Global COVID-19 clinical platform [2], which observed 15% higher odds of severe/critical presentation and 38% increased odds of death among patients with HIV compared to those without HIV, after adjusting for multiple confounders including comorbidities. However, the study was restricted to those hospitalized with COVID-19. The largest study specific to CYPHIV to date was of 60 individuals in a Spanish paediatric HIV cohort (included here), which reported 8 (13%) cases diagnosed with SARS-CoV-2 [9].

There are important study limitations. Firstly, availability of SARS-CoV-2 PCR testing varied across countries over time and asymptomatic infections were likely missed, leading to an underestimation of incidence. In comparison, a serology study of ~500 participants from the EPPICC cohort reported 55% were seropositive by mid-2022 [10]. Further, no data on potentially 'silent' symptoms of MIS-C, such as myocarditis, were available. However, we are confident that severe cases would have been reported to HIV clinics and captured here, so our conclusion of SARS-CoV-2 infection being overwhelmingly mild in this cohort is likely correct. Secondly, dates of SARS-CoV-2 infection and clinical details were not available for all cases. Thirdly, small numbers of cases meant estimating rates of infection over time was not possible. Finally, data on SARS-CoV-2 vaccination were not collected, as data collection began before rollout.

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Conflicts of interest

Marisa Luisa Navarro has collaborated in educational activities supported by Gilead, GlaxoSmithKline, MSD, Pfizer, Sanofi Pasteur, Janssen, ViiV Healthcare and as an investigator in clinical trials for GlaxoSmithKline, Janssen, MSD, Pfizer, Sanofi; and as a consultant on GlaxoSmithKline Advisory Boards and research grants of GILEAD, ISCIII and IISGM of Spain. All other authors declare no conflicts of interest.

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