

A Post-Pandemic Surge in Pediatric Epstein–Barr Virus Infection: A Six-Year Single- Center Retrospective Study in China, 2019–2024

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Abstract

Background

The COVID-19 pandemic has altered the epidemiology of numerous childhood pathogens, but its effect on pediatric Epstein–Barr virus (EBV) infection remains poorly defined due to a lack of multi-year laboratory data outside a few centers.

Methods

We initially collected a total of 51,056 EBV-DNA PCR records from pediatric patients at Hebei Children's Hospital (2019–2024). After exclusions, 30,254 specimens were included in the final analysis. These patients were stratified into three epidemiological periods: pre-COVID-19 (2019), during COVID-19 (2020–2022), and post-COVID-19 (2023–2024).

Results

Overall positivity was 14.26% (4,313/30,254), increasing from 10.45% pre-pandemic to 12.83% during and 17.44% post-pandemic ($p < 0.001$). Viral loads and patient age also increased across periods (both $p < 0.001$). The post-COVID-19 period was an independent risk factor (adjusted OR = 1.87, 95% CI: 1.68–2.07). Pneumonia and upper respiratory tract infections were more common post-COVID-19.

Conclusions

In line with reports from other Chinese medical centers, these findings reveal a sustained post-COVID-19 surge in pediatric active EBV infection and a concurrent age shift toward school-aged children, highlighting the need for continued heightened surveillance in this population.

1. Introduction

Epstein-Barr virus (EBV) is a double-stranded DNA virus of the *Gammaherpesvirinae* subfamily. Humans are the sole natural host, and transmission occurs predominantly via saliva. Seroprevalence surveys indicate that more than 90% of adults worldwide are lifelong carriers[1–3]. Primary infection in infancy and early childhood is largely asymptomatic, whereas infection acquired later in childhood or adolescence more often presents as infectious mononucleosis, characterized by fever, pharyngitis, and lymphadenopathy[4]. EBV has additionally been implicated in a range of lymphoproliferative, oncologic, and autoimmune conditions[5–9]. After primary infection, EBV establishes lifelong latency in B lymphocytes and oropharyngeal epithelium, with reactivation occurring when host immunity is compromised; both primary infection and reactivation are detectable as active infection by peripheral blood EBV-DNA testing[10–12].

Non-pharmaceutical interventions (NPIs) adopted in China during the COVID-19 pandemic effectively reduced the transmission of numerous respiratory and contact-transmitted pathogens[13–15]. After the relaxation of these measures at the end of 2022, a nationwide surge of SARS-CoV-2 infections ensued, followed by a sharp rebound in multiple pediatric infectious diseases—and throughout 2023 and 2024, SARS-CoV-2 continued to resurge in repeated but progressively smaller waves[16, 17]. A recent single-centre study from Hangzhou (Li et al., 2026) reported a sustained post-pandemic increase in pediatric EBV positivity, a shift in age of onset towards school-aged children, and an altered clinical spectrum of active EBV infection[1]. Whether this epidemiological pattern is reproducible in other pediatric populations, and whether its magnitude is comparable across regions, remain open questions that call for broader, multi-centre data.

In this study, we analyzed six years (2019–2024) of peripheral blood EBV-DNA PCR testing data from Hebei Children's Hospital, spanning the pre-, during-, and post-COVID-19 periods. Our aim was to characterize the epidemiological trajectory of pediatric active EBV infection in this region and to compare our findings with those reported from other Chinese centers, thereby providing reference for regional surveillance and clinical practice.

2. Materials and Methods

2.1. Study Design and Patients

This retrospective study included all pediatric patients who underwent EBV-DNA PCR testing at Hebei Children's Hospital between January 2019 and December 2024 ($n = 51,056$ test records). Inclusion criteria were: (1) age < 18 years; (2) peripheral blood specimen. Records from cerebrospinal fluid, urine, bronchoalveolar lavage fluid, and other non-blood specimens ($n = 6,601$), as well as those from patients aged ≥ 18 years ($n = 149$, predominantly parents or accompanying adults tested alongside a child), were excluded, leaving 44,306 blood-specimen records from pediatric patients. Qualitative results reported as equivocal ("grey zone", recommended for retest) were also excluded from the primary analysis ($n = 375$). For each patient with more than one record over the study period, the first positive result (if any) was used; otherwise, the first negative result was used, consistent with the approach adopted by Li et al.[1]. Ultimately, 30,254 specimens were included in the final analysis (Fig. 1). Patients were divided into six age groups: 0–6 months, 6 months–1 year, 1–3 years, 3–6 years, 6–12 years and > 12 years.

2.2. Laboratory Testing

Peripheral blood EBV-DNA was measured by real-time fluorescence quantitative PCR performed by the hospital's clinical laboratory as part of routine care. From January 2019 to January 2024, samples with EBV-DNA ≥ 250 copies/ml were reported as positive; from February 2024 onward, following a reagent-kit change, the reporting cutoff was revised to ≥ 500 copies/ml. Both assay versions additionally reported an equivocal ("grey zone") category for detectable but sub-threshold amplification, which was excluded from the primary positivity analysis as described above. This assay change over the study period is acknowledged as a limitation (see Discussion).

2.3. Statistical Analysis

Statistical analyses were performed using Python (pandas, scipy). Categorical variables were compared using the chi-square test. Differences in continuous variables (age and viral load) across the three periods were assessed using the Kruskal–Wallis test. Multivariable logistic regression (fitted via iteratively reweighted least squares) was used to identify independent factors associated with active EBV infection, adjusting simultaneously for pandemic period, sex, and age group; Results are expressed as adjusted odds ratios (ORs) with 95% Wald confidence intervals (CIs). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic Characteristics

A total of 30,254 pediatric patients with a definitive EBV-DNA result were included: 5,110 in the pre-COVID-19 period (2019), 13,160 during COVID-19 (2020–2022), and 11,984 post-COVID-19 (2023–2024). Overall, 59.36% of patients were male and the median (IQR) age was 48 (12,96) months. The overall EBV-DNA positivity rate was 14.26% (4,313/30,254).

The proportion of male patients did not differ significantly across the three periods ($p > 0.05$). But it was noted that the number of patients in school-aged and adolescent groups increased markedly. The age distribution shifted rightward, with median age increasing from 36 (12, 72) months in the pre-COVID-19 period to 48 (12, 84) months during COVID-19 and 60 (24, 108) months in the post-COVID-19 period ($p < 0.001$) (Table 1).

Table 1

Total patient characteristics and EBV-DNA positivity in the pre-, during-, and post-COVID-19 periods.

Characteristic	Pre-COVID-19 (2019) (n = 5,110)	During COVID-19 (2020–2022) (n = 13,160)	Post-COVID-19 (2023–2024) (n = 11,984)	p- Value
Male sex, n (%)	3092 (60.51)	7820 (59.42)	7046 (58.80)	> 0.05
Age, median (IQR), month	36 (12, 72)	48 (12, 84)	60 (24, 108)	< 0.001
Age groups, n (%)				< 0.001
0–6 months	593 (11.60)	1342 (10.20)	605 (5.05)	
6 months–1 year	403 (7.89)	964 (7.33)	537 (4.48)	
1–3 years	1264 (24.74)	2825 (21.47)	1859 (15.51)	
3–6 years	1347 (26.36)	3385 (25.72)	3082 (25.72)	
6–12 years	1237 (24.21)	3503 (26.62)	4490 (37.47)	
>12 years	266 (5.21)	1141 (8.67)	1411 (11.77)	
EBV DNA positivity, n (%)	534 (10.45)	1689 (12.83)	2090 (17.44)	< 0.001
<i>IQR, interquartile range; EBV, Epstein–Barr virus.</i>				

3.2. Demographic Characteristics and Viral Load Profiles of EBV-Positive Patients

EBV-DNA positivity rates increased in a stepwise manner, from 10.45% (534/5110) pre-COVID-19 to 12.83% (1689/13,160) during COVID-19 and 17.44% (2090/11,984) post-COVID-19 ($p < 0.001$) (Table 1). Among EBV-DNA-positive patients, viral load differed significantly across periods ($p < 0.001$), with median (IQR) load rising from 3,152 (1,019–8,462) copies/ml pre-COVID-19 to 4,333 (1,364–14,330) copies/ml during COVID-19, then declining slightly to 4,027 (1,324–12,760) copies/ml post-COVID-19 – though still remaining above the pre-pandemic level (Table 2); In parallel, median age among positive patients also increased progressively (Table 2), from 42 (24, 60) months pre-COVID-19 to 48 (24, 72) months during COVID-19 and 60 (36, 84) months post-COVID-19 ($p < 0.001$).

Table 2

Characteristics and DNA loads of EBV-DNA-positive pediatric patients in the pre-, during-, and post-COVID-19 periods.

Characteristic	Pre-COVID-19 (2019) (n = 534)	During COVID-19 (2020–2022) (n = 1,689)	Post-COVID-19 (2023–2024) (n = 2,090)	p-Value
Male sex, n (%)	345 (64.61)	943 (55.83)	1216 (58.18)	0.002
Age, median (IQR), month	42 (24, 60)	48 (24, 72)	60 (36, 84)	< 0.001
EBV DNA load				< 0.001
Median (copies/mL)	3,152	4,333	4,027	
IQR (copies/mL)	1,019–8,462	1,364–14,330	1,324–12,760	
<i>IQR, interquartile range; EBV, Epstein–Barr virus.</i>				

3.3. Monthly Variation in EBV Infection

As shown in Fig. 1, both testing volume and the number of positive cases increased substantially from 2023 onward. Monthly positivity rates rose from a fluctuating range of approximately 8–15% during 2019–2022 to frequently exceeding 20% in 2023–2024, with several months even surpassing 25%. In the post-COVID-19 period, EBV infection peaks were predominantly observed in July, August or September, whereas troughs occurred mostly in December or January (Fig. 2).

3.4. Age Group Variation in EBV Infection

In the pre-COVID-19 period, active EBV infection was concentrated in children aged 1–3 years and 3–6 years, who together accounted for 75.10% of positive cases, whereas the two youngest groups (< 6 months and 6 months–1 year) combined represented only 3.74%. This age distribution also persisted during the COVID-19 pandemic, with 1- to 3-year and 3- to 6-year age groups together comprising 71.05% of positive cases. In the post-COVID-19 period, however, the age composition shifted markedly toward older children: the proportion of positive cases in the 6- to 12-year age group rose from 20.79% pre-COVID-19 to 35.45% post-COVID-19, and that in adolescents (> 12 years) increased more than 10-fold, from 0.37% to 4.02% (Fig. 3, Fig. 4). Correspondingly, the combined proportion of positive cases in children younger than 3 years decreased from 37.45% pre-COVID-19 to 21.29% post-COVID-19 (Fig. 3, Fig. 4).

3.5. Factors Associated with EBV Infection

After adjusting for period, sex, and age group, multivariable logistic regression confirmed all three as independent factors associated with active EBV infection (Table 3). Compared with the pre-COVID-19 baseline, the risk of infection was higher during COVID-19 (adjusted OR = 1.31, 95% CI 1.18–1.45, $p < 0.001$) and highest post-COVID-19 (adjusted OR = 1.87, 95% CI 1.68–2.07, $p < 0.001$). Females had a

slightly higher risk than males (adjusted OR = 1.10, 95% CI: 1.03–1.17, $p = 0.007$); although statistically significant, the effect size was small, indicating no clinically meaningful sex difference in EBV infection. Using infants younger than 6 months as the reference, infection risk rose sharply with age: adjusted OR = 12.01 (95% CI 6.41–22.48, $p < 0.001$) for infants(6 months–1 year), and increased further to a peak of OR = 63.25 (95% CI 34.89–114.64, $p < 0.001$) among preschool-aged group (3–6 years). Risk remained markedly elevated, though somewhat lower than the peak, in the toddlers (1–3 years) (OR = 49.25, 95% CI 27.14–89.39, $p < 0.001$) and School-aged children (OR = 32.38, 95% CI 17.85–58.75, $p < 0.001$). Among all age groups, the smallest risk increase was observed in adolescents (> 12 years) (adjusted OR = 9.06, 95% CI: 4.88–16.85, $p < 0.001$).

Table 3
Multivariable logistic regression analysis of factors associated with EBV infection.

Characteristic	Adjusted OR	95% CI	<i>p</i> -Value
Period (Reference: Pre-COVID-19)			
During COVID-19	1.31	1.18–1.45	< 0.001
Post-COVID-19	1.87	1.68–2.07	< 0.001
Sex (Reference: Male)			
Female	1.10	1.03–1.17	0.007
Age Group (Reference: 0–6 months)			
6 months–1 year	12.01	6.41–22.48	< 0.001
1–3 years	49.25	27.14–89.39	< 0.001
3–6 years	63.25	34.89–114.64	< 0.001
6–12 years	32.38	17.85–58.75	< 0.001
>12 years	9.06	4.88–16.85	< 0.001
<i>EBV, Epstein–Barr virus; OR, odds ratio; CI, confidence interval. Adjusted for period, sex, and age group simultaneously.</i>			

3.6. Initial Diagnoses of EBV-DNA-Positive Pediatric Patients

Initial diagnoses associated with EBV-DNA-positive test orders were extracted from the recorded clinical diagnosis field, which could contain more than one concurrent diagnosis per patient; consequently, category proportions in Table 4 are not mutually exclusive. Infectious mononucleosis remained the single most common associated diagnosis in all three periods but declined in relative proportion after the pandemic (33.52% pre-COVID-19 vs. 27.03% post-COVID-19, $p = 0.012$). The proportions of patients with pneumonia (4.12% vs. 7.32%, $p = 0.005$) and upper respiratory tract infection (4.12% vs. 8.52%, $p = 0.002$) were significantly higher post-COVID-19 than pre-COVID-19, while tonsillitis (9.74% vs. 8.61%, $p =$

0.005), lymphadenopathy / lymphadenitis (10.67% vs. 7.51%, $p = 0.030$), and liver impairment (2.62% vs. 1.82%, $p < 0.001$) declined. Cytopenia, allergic dermatitis, gastroenteritis, hemophagocytic syndrome and cardio-cerebro-renal disease did not differ significantly across periods in our cohort (Table 4).

Table 4

Variation in initial diagnoses of EBV-DNA-positive pediatric patients in the pre-, during-, and post-COVID-19 periods.

Initial Diagnosis	Pre n	Pre %	During n	During %	Post n	Post %	p- Value
Infectious mononucleosis	179	33.52	479	28.36	565	27.03	0.012
Fever	104	19.48	275	16.28	345	16.51	0.203
Pneumonia	22	4.12	90	5.33	153	7.32	0.005
Tonsillitis	52	9.74	199	11.78	180	8.61	0.005
Upper respiratory infection	22	4.12	148	8.76	178	8.52	0.002
Lymphadenopathy/lymphadenitis	57	10.67	123	7.28	157	7.51	0.030
Cytopenia	11	2.06	52	3.08	65	3.11	0.417
Liver impairment	14	2.62	72	4.26	38	1.82	< 0.001
Allergic dermatitis	0	0.00	3	0.18	1	0.05	0.322
Gastroenteritis/enteritis	0	0.00	4	0.24	9	0.43	0.222
Hemophagocytic syndrome	0	0.00	8	0.47	3	0.14	0.062
Cardio-cerebro-renal disease	1	0.19	19	1.13	15	0.72	0.087
<i>Diagnosis categories are not mutually exclusive (patients could carry more than one recorded diagnosis); percentages are calculated within each period's positive patients and therefore may sum to more than 100%.</i>							

4. Discussion

This six-year, single-center analysis demonstrates a sustained post-COVID-19 surge in pediatric active EBV infection, characterized by rising positivity, a marked age shift toward school-age children and changes in the associated clinical spectrum. These findings are broadly consistent with those recently reported by Li et al. from Hangzhou [1], who observed positivity rising from 13.55% pre-COVID-19 to 22.83% post-COVID-19, an age shift toward children aged 6–11 years, and increased proportions of pneumonia among EBV-positive patients. In our cohort, positivity rose from 10.45% to 17.44% across the same relative periods, and the adjusted odds of post-COVID-19 infection (OR = 1.87) closely mirrored the previously reported estimate (OR = 1.81), as did the modestly elevated risk in female patients (OR = 1.10 vs. 1.10) and the pattern of age-group risk, which peaked in the 3–6-year age band (equivalent to the 3–

5-year band used in the original report) in both cohorts. Additional domestic multi-center EBV epidemiological research also confirmed age shift features in Chinese hospitalized children before and after the pandemic[18, 19]. This convergence across two independent pediatric populations in China strengthens the evidence that the post-COVID-19 EBV surge is a generalizable phenomenon rather than a center-specific anomaly. Studies of other post-pandemic pathogens in Chinese children, including common respiratory viruses[13, 15, 16, 20] and macrolide-resistant *Mycoplasma pneumoniae*[14, 21], have documented similarly shaped post-pandemic resurgences, commonly attributed in part to an accumulated "immune debt" of reduced early-life pathogen exposure during the NPIs period[22]. These observations provide a broader epidemiological context for the EBV-specific findings reported here and in the Hangzhou cohort[1].

Several explanations have been proposed for this phenomenon. Pandemic-era NPIs likely delayed primary EBV infection in a substantial proportion of susceptible young children, generating an accumulated pool of EBV-naïve children who then experienced a concentrated wave of primary infection once social contact resumed[16, 19, 23]. However, the sustained elevation in positivity across two full years after the initial rebound, observed both in our data and in the Hangzhou cohort, suggests that a simple rebound in primary infection is unlikely to be the sole mechanism. Several recent reviews and mechanistic studies have proposed that recurrent SARS-CoV-2 infections may drive repeated reactivation of latent EBV, potentially through post-infectious immune dysregulation and host interleukin-1 pathway-related genetic factors, as a contributing mechanism[24–27]. COVID-19 infection and vaccines are considered potential triggers for reactivation of the *Herpesviridae* family[28]. Multiple clinical studies have confirmed elevated EBV viral load in COVID-19 infected patients with impaired lymphocyte subpopulations and immune function[29–31], and long-term immunological dysfunction following mild SARS-CoV-2 infection may further facilitate *Herpesviridae* reactivation[32]. And a comparative meta-analysis in hospitalized adults found EBV reactivation during acute COVID-19 to be associated with excess mortality[33]. However, direct evidence supporting this reactivation pathway remains lacking.

Unlike the original Hangzhou report, we did not observe a sustained increase in viral load across all three periods. In our cohort, median viral load rose from pre-COVID-19 to during-COVID-19 but declined slightly in the post-COVID-19 period, coinciding with a change in the reporting assay's quantification cutoff in February 2024, which may partly explain this discrepancy and should be interpreted with caution. We also did not reproduce the previously reported increase in allergic dermatitis; using the strict diagnostic label "allergic dermatitis", this diagnosis was rare throughout our cohort ($\leq 0.18\%$ in any period) and even a broadened definition including rash-related diagnoses showed no significant trend. Notably, a recent single-center pediatric study from Argentina reported the opposite epidemiological pattern – a decrease rather than an increase in EBV positivity after the pandemic – underscoring that findings from any single cohort, including ours, should not be assumed to generalize without corroboration from additional populations[23]. Differences in local diagnostic coding practice, in which cutaneous manifestations may more often be recorded as "rash" than as a specific dermatologic diagnosis, may also contribute to the discrepancy observed for allergic dermatitis.

Consistent with the original report, pneumonia and upper respiratory tract infection were significantly more frequent among EBV-positive patients in the post-COVID-19 period, which may reflect both a genuine shift in the clinical presentation of pediatric EBV infection and closer co-circulation with other post-pandemic respiratory pathogens[34]. The marked age shift toward school-aged children observed in both cohorts likely reflects delayed primary infection during the NPIs period combined with the greater likelihood that older, symptomatic children will present for medical evaluation and undergo EBV-DNA testing, whereas infection in younger children is more often subclinical.

This study has several limitations. It is a retrospective, single-center analysis and may not generalize to other regions or hospital settings. The reporting cutoff of the EBV-DNA assay changed partway through the post-COVID-19 period (from ≥ 250 to ≥ 500 copies/ml in February 2024), which may have introduced some discontinuity into the viral-load trend but had a relatively minor impact on the positivity trend. Initial diagnosis was extracted from a multi-label clinical diagnosis field rather than a single adjudicated primary diagnosis, so diagnosis proportions in Table 4 are not mutually exclusive and are not directly comparable in absolute magnitude to single-diagnosis classifications used elsewhere. Finally, as in the original report, EBV-DNA detection cannot distinguish primary infection from reactivation, and information on patients' SARS-CoV-2 infection history was not available, precluding direct testing of the reactivation hypothesis.

5. Conclusions

In this six-year, single-center pediatric cohort, active EBV infection showed a sustained post-pandemic surge characterized by higher positivity, a pronounced shift toward school-aged children, and an increased proportion of pneumonia and upper respiratory tract infection among positive patients. These findings closely parallel those recently reported from another major Chinese pediatric center[1, 19]. They support continued heightened surveillance of EBV infection in school-aged children in the post-COVID-19 period and call for multi-center, prospective studies to clarify the mechanisms underlying this sustained surge.

Abbreviations

EBV
Epstein-Barr virus
COVID-19
Coronavirus Disease 2019
SARS-CoV-2
Severe Acute Respiratory Syndrome Coronavirus2
PCR
Polymerase Chain Reaction
NPIs
Non-pharmaceutical Interventions

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hebei Children's Hospital (Approval No.: Medical Research Ethics Review No. 201) and was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

This retrospective study only collected and analyzed existing medical records from previous clinical diagnosis and treatment at Hebei Children's Hospital. It did not involve any prospective intervention, additional examinations, or follow-up procedures for the study participants. The risk to participants is no greater than minimal risk, and the waiver of informed consent will not adversely affect the rights or health of the participants. All personally identifiable information was de-identified prior to analysis, and participants' privacy and personal data were strictly protected.

Data Availability Statement

The data supporting this study are not publicly available due to legal and institutional restrictions concerning patient privacy and confidentiality.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

Conceptualization, F.M. and J.Y.; methodology, X.Z. and L.Z.; formal analysis, L.Z.; data curation, S.G. and L.Z.; writing-original draft preparation, X.Z. and L.Z.; writing-review and editing, X.Z. and S.G. All authors have read and agreed to the published version of the manuscript.

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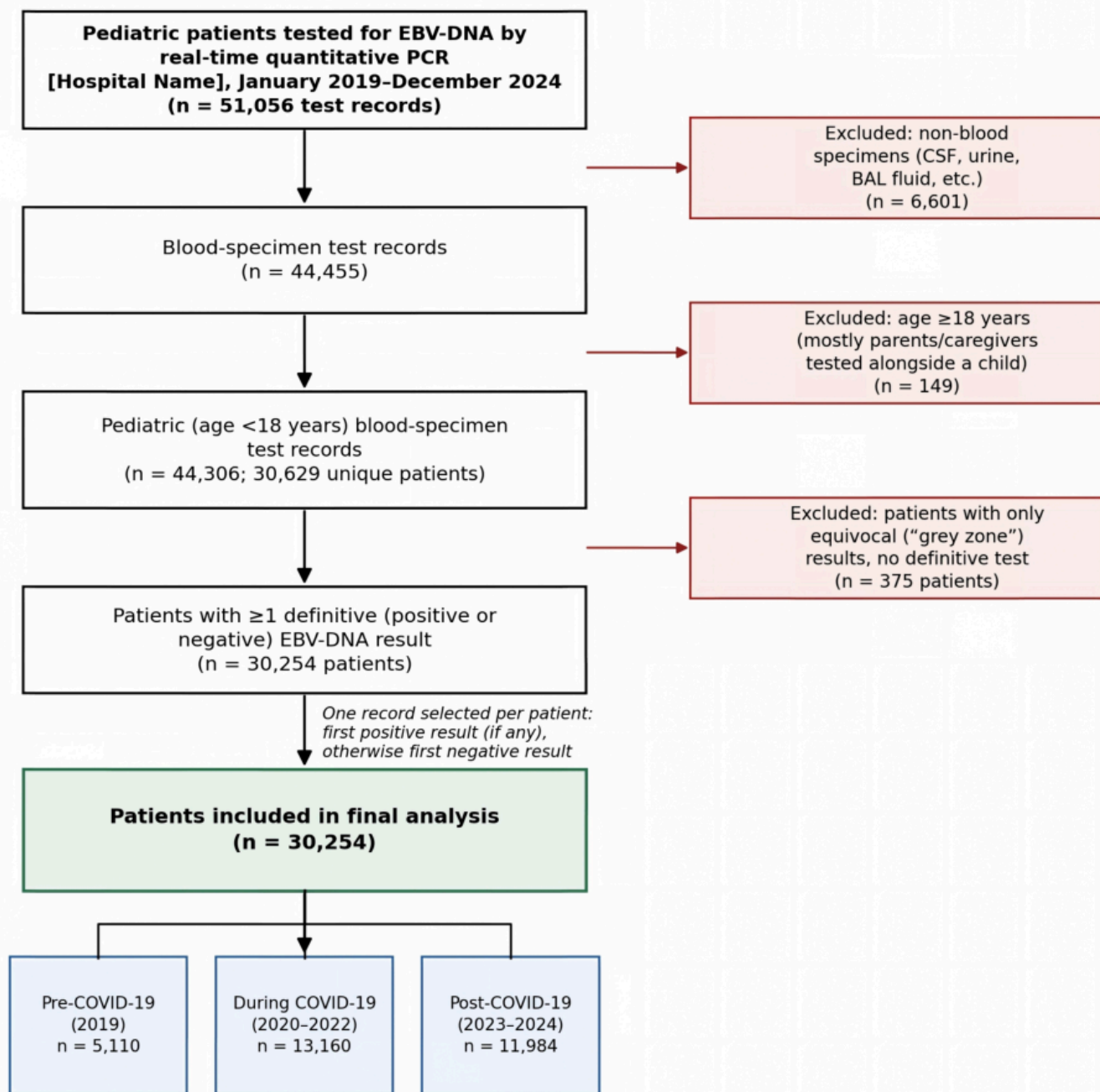
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Figures



Flowchart of patient selection for this retrospective EBV-DNA study

Figure 1

Legend not included with this version

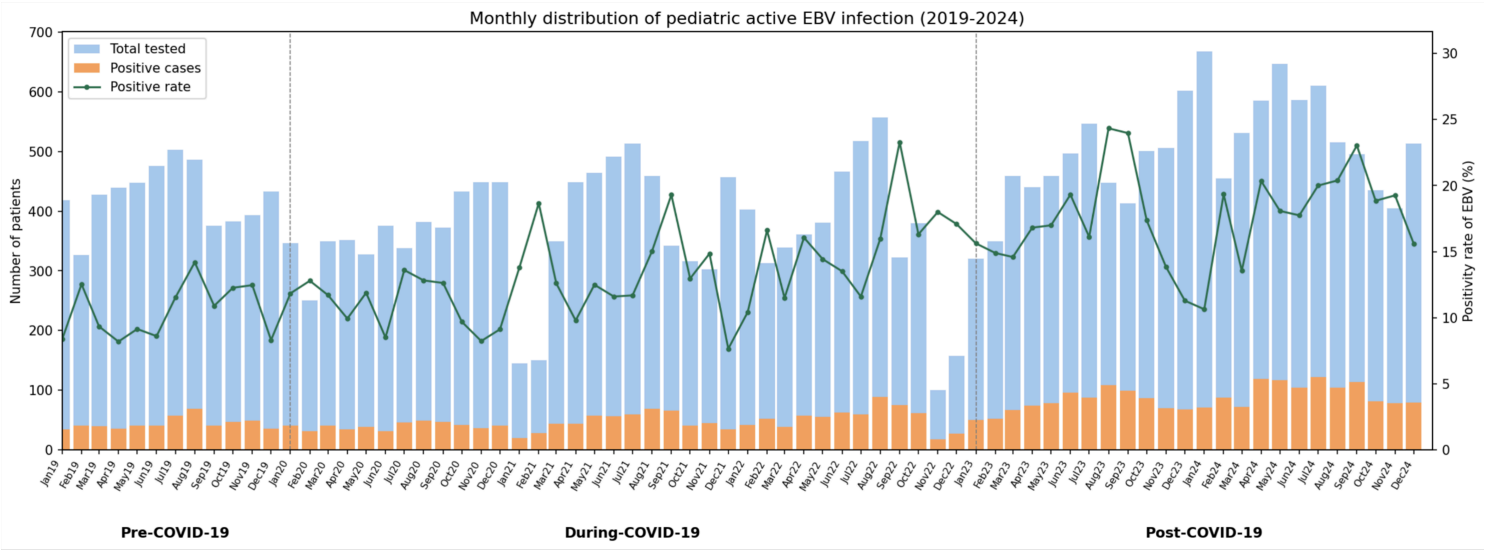


Figure 2

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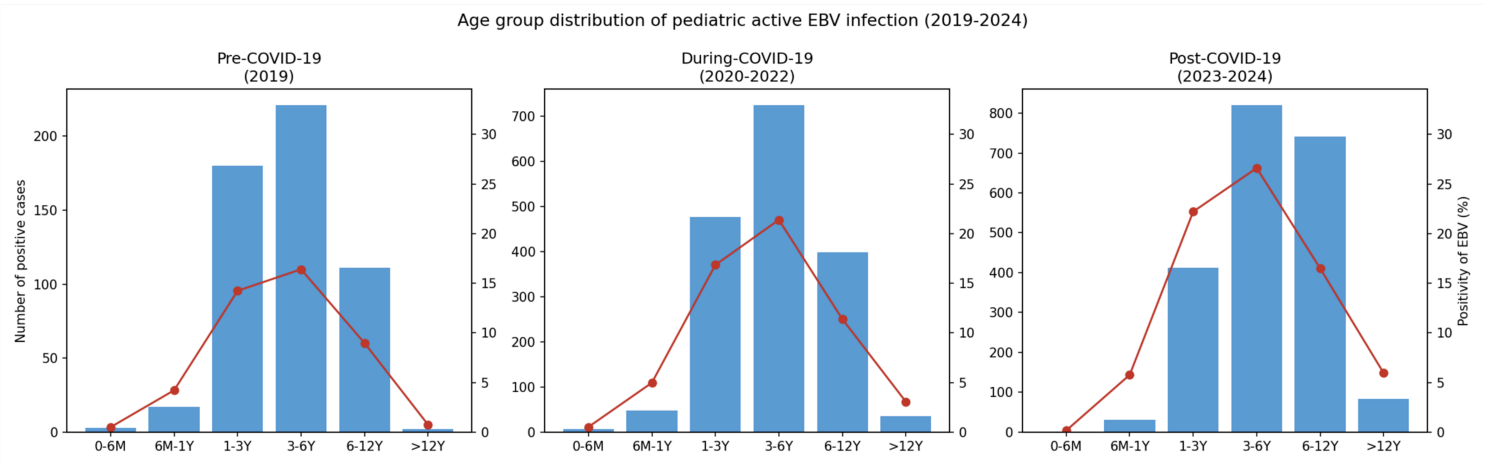


Figure 3

Legend not included with this version

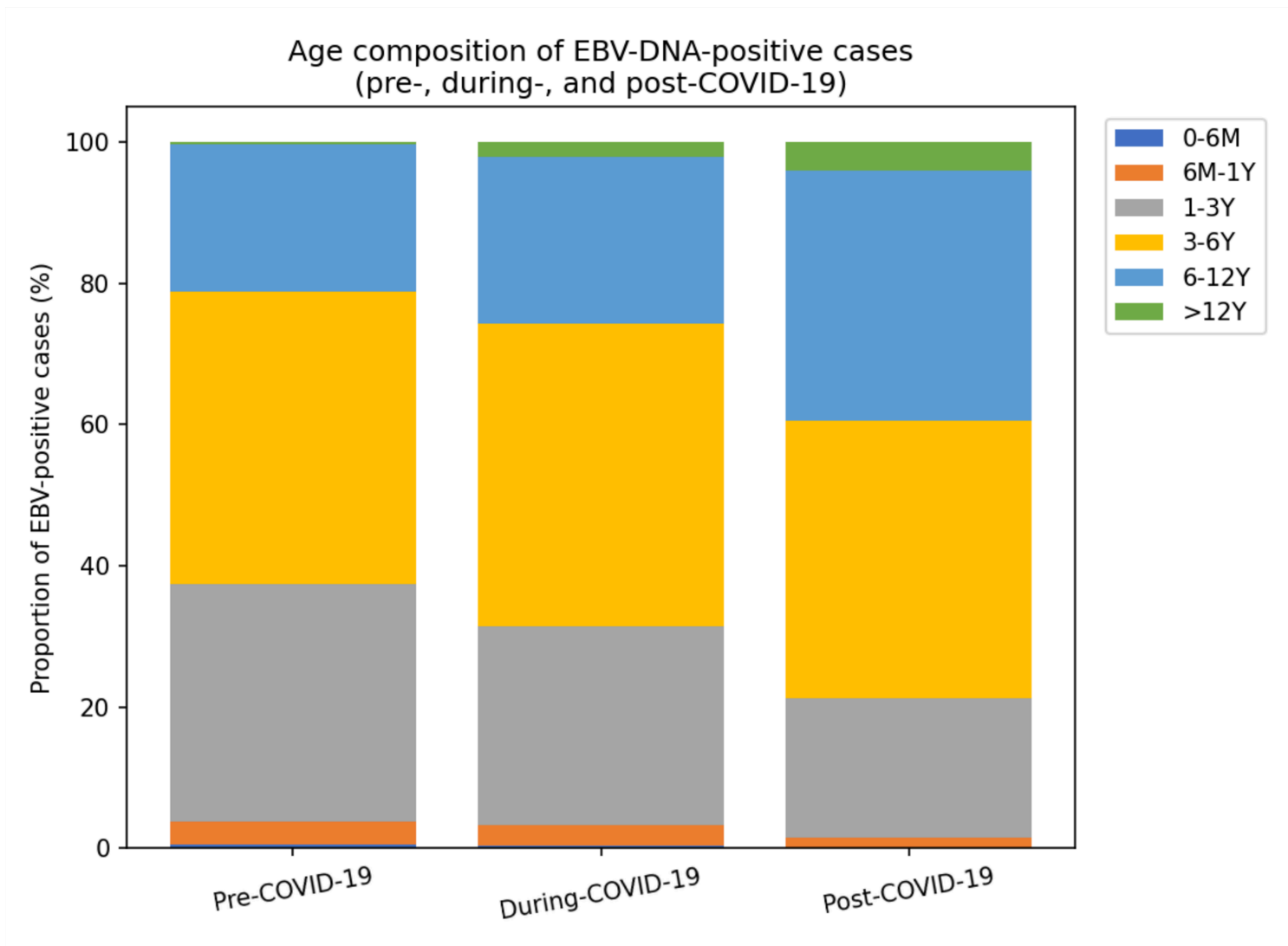


Figure 4

Legend not included with this version