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Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 Emergence Amidst Community-Acquired Respiratory Viruses

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Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China as the cause of coronavirus disease 2019 in December 2019 and reached Europe by late January 2020, when community-acquired respiratory viruses (CARVs) are at their annual peak. We validated the World Health Organization (WHO)–recommended SARS-CoV-2 assay and analyzed the epidemiology of SARS-CoV-2 and CARVs.

Methods. Nasopharyngeal/oropharyngeal swabs (NOPS) from 7663 patients were prospectively tested by the Basel S-gene and WHO-based E-gene (Roche) assays in parallel using the Basel N-gene assay for confirmation. CARVs were prospectively tested in 2394 NOPS by multiplex nucleic acid testing, including 1816 (75%) simultaneously for SARS-CoV-2.

Results. The Basel S-gene and Roche E-gene assays were concordant in 7475 cases (97.5%) including 825 (11%) SARS-CoV-2 positives. In 188 (2.5%) discordant cases, SARS-CoV-2 loads were significantly lower than in concordant positive ones and confirmed in 105 (1.4%). Adults were more frequently SARS-CoV-2 positive, whereas children tested more frequently CARV positive. CARV coinfections with SARS-CoV-2 occurred in 1.8%. SARS-CoV-2 replaced CARVs within 3 weeks, reaching 48% of all detected respiratory viruses followed by rhinovirus/enterovirus (13%), influenza virus (12%), coronavirus (9%), respiratory syncytial virus (6%), and metapneumovirus (6%).

Conclusions. Winter CARVs were dominant during the early SARS-CoV-2 pandemic, impacting infection control and treatment decisions, but were rapidly replaced, suggesting competitive infection. We hypothesize that preexisting immune memory and innate immune interference contribute to the different SARS-CoV-2 epidemiology among adults and children.

Keywords. COVID-19; respiratory virus; multiplex; nucleic acid testing; coinfection.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China during winter 2019 as a new cause of severe viral pneumonia, called coronavirus infectious disease (COVID-19) [1, 2]. Since late January 2020, SARS-CoV-2 continues to spread across the world including in Europe [1, 3]. By 14 July 2020, the World Health Organization (WHO) reported >13 million confirmed SARS-CoV-2 cases and nearly 600 000 deaths, of which approximately one-third occurred in Europe [4]. The first case in Switzerland was diagnosed on 25 February 2020, reaching peak rates by the end of March before plateauing at approximately 30 000 confirmed cases by the end of April 2020 (https://covid-19-schweiz.bagapps.ch/de-2.html). Notably, the initial pandemic spread of SARS-CoV-2 occurred in the winter months of the Northern Hemisphere, during which several community-acquired respiratory viruses (CARVs) are known to circulate including influenza virus A/B, respiratory syncytial virus (RSV), metapneumovirus, parainfluenza virus (PIV), and human coronaviruses (HCoVs). Although the progression of SARS-CoV-2 infection to severe lower respiratory tract infectious disease is unprecedented, all CARVs are known to significantly contribute to seasonal excess morbidity and mortality in immunocompetent and immunocompromised populations [5]. In fact, CARV respiratory tract infectious disease presents clinically as an influenza-like illness, defined as at least 1 respiratory and 1 systemic symptom/sign such as clogged or runny nasal airways, sore throat, cough,

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fatigue, fever, and myalgia [5], which may be indistinguishable from early stages of SARS-CoV-2 infection [6], while dysgeusia appears to be rather prominent. Thus, a broad diagnostic approach using multiplex nucleic acid testing (NAT) may be important. Notably, the course and impact of SARS-CoV-2 on circulating CARVs has not been fully characterized. Early reports suggested that coinfections with SARS-CoV-2 and other CARVs were rather uncommon in immunocompetent adults [7]. However, a recent study reported coinfection of CARVs and SARS-CoV-2 at rates of 5% including influenza virus A/B, RSV, and rhinoviruses [8]. Here, we report on the epidemiology of SARS-CoV-2 infection and other CARVs during the early pandemic peak in northwestern Switzerland from 1 January until 29 March 2020.

MATERIALS AND METHODS

Patients and Samples

Patients presenting with influenza-like illness to the outpatient department or emergency department of the University Hospital Basel or the University of Basel Children's Hospital were enrolled in this retrospective analysis of prospectively collected data on respiratory virus panel and/or SARS-CoV-2 testing between 1 January and 29 March 2020.

Clinical Samples and Total Nucleic Acid Extraction

For sampling, 2 swabs from the nasopharyngeal and oropharyngeal sites (NOPS), respectively, were taken and combined into 1 universal transport medium tube (UTM, Copan). In smaller children, only nasopharyngeal swabs were taken. Total nucleic acids (TNAs) were extracted from the UTM using the MagNA Pure 96 system and the DNA and viral NA small volume kit (Roche Diagnostics, Rotkreuz, Switzerland) or using the Abbott m2000 Realtime System and the Abbott sample preparation system reagent kit (Abbott, Baar, Switzerland).

SARS-CoV-2 Reverse-Transcription Quantitative Nucleic Acid Testing

TNAs were tested for SARS-CoV-2 RNA using a laboratory-developed reverse-transcription quantitative nucleic acid test (RT-QNAT) targeting specific viral sequences of the spike glycoprotein S-gene (Basel SCoV2-S-111bp) and a commercial RT-QNAT targeting the viral envelope gene (E-gene; Roche). For details, see Supplementary Table 1.

Phylogenetic Analysis of SARS-CoV-2 Genome Sequences

SARS-CoV-2 was based on the viral reference genome (accession number NC_045512) as detailed in Supplementary Table 2, as described previously [9].

Biofire Filmarray Respiratory Panel

The qualitative multiplex NAT respiratory panel used 200 µL of UTM in the Torch system (Biofire Filmarray respiratory 2.0 panel, bioMérieux) covering influenza viruses A (H1, H1/2009, and H3) and B; human RSV A and B; adenovirus; human metapneumovirus; rhinovirus/enterovirus; PIV 1–4 (as separate targets); HCoVs (NL63, 229E, OC43, HKU1, and Middle East respiratory syndrome); *Bordetella pertussis*; *Bordetella parapertussis*; *Chlamydophila pneumoniae*; and *Mycoplasma pneumoniae*.

Statistics and Graphical Presentations

All statistical data analyses were done in R software (https://www.r-project.org/), and Prism version 8 (GraphPad Software) was used for data visualization. Statistical comparison of nonparametric data was done using Mann–Whitney *U* test, and Bonferroni correction was applied for multiple comparisons.

Ethics Statement

The study was conducted according to good laboratory practice and in accordance with the Declaration of Helsinki and national and institutional standards, and was approved by the ethical committee (EKNZ 2020-00769).

RESULTS

To independently evaluate the WHO-recommended assay, we designed 2 different single-step RT-QNAT assays targeting the S-gene and the N-gene. We observed close clustering of the complete SARS-CoV-2 genomes and specifically its S- and N-gene target sequences, clearly separating from the corresponding HCoV genome sequences (Supplementary Figure 1). We found no insertions or deletions in either target, and only a single single-nucleotide polymorphism in the probe-binding site of the S-gene RT-QNAT in 1 of 3323 (0.03%) sequences, at a central position not predicted to affect the assay performance (Supplementary Table 2).

To cross-validate the WHO–Roche E-gene and the Basel S-gene without reporting delay, we tested all submitted NOPS prospectively in parallel. In the first phase of the pandemic, SARS-CoV-2 testing was restricted to symptomatic patients in Switzerland. From 9 to 29 March 2020 (calendar weeks 11–13), 7663 samples were submitted from 354 (5%) pediatric and 7309 (95%) adult patients (Table 1). Most patients had presented to primary care (74%), whereas 26% of cases originated from secondary and tertiary care units including outpatients as well as admission to medical units (7%) and intensive care (3%) (Table 1). The Basel S-gene and the Roche E-gene RT-QNATs were concordant in 7475 (97.5%) samples, consisting of 6650 (86.8%) negative and 825 (10.7%) positive cases, all of which were independently confirmed by the N-gene assay (Supplementary Figure 2). In 188 (2.5%) cases, discordant results were obtained consisting of 170 (2.2%) Basel S-gene–positive/Roche E-gene–negative, and 18 (0.2%) Basel S-gene–negative/Roche E-gene–positive cases. The N-gene RT-QNAT confirmed 102 of 170 (60%; overall 1.3%) of the former, but only 3 (0.04%) of the latter (Supplementary Figure 2). Cycle threshold (Ct) values were significantly lower in these samples, indicating a higher viral load for concordant positive than for discordant results (median

Table 1. Patient Demographics of Nasopharyngeal/Oropharyngeal Swabs Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Between Calendar Weeks 11 and 13, 2020 (N = 7663)

Characteristic	All	SARS-CoV-2 Positive	SARS-CoV-2 Negative	*P* Value[a]
Patient demographics				
No. of patients	7663	930 (12)	6733 (88)	
Age, y, median	43	49	43	<.001
25th, 75th percentile (IQR)	31, 58 (27)	34, 62 (28)	30, 57 (27)	
Sex, male	3407 (44)	458 (49)	2949 (44)	.002
Pediatric patients (≤16 y)	354 (5)	14 (4)	340 (96)	<.001
Primary care	5697 (74)	774 (83)	4923 (73)	
Secondary or tertiary care	1966 (26)	156 (17)	1810 (27)	
Medical care unit	136 (7)	11 (7)	125 (7)	
Intensive care unit	67 (3)	8 (5)	59 (3)	
Pneumology unit	45 (2)	1 (1)	44 (2)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Groups were compared using Mann–Whitney *U* test.

for S-gene RT-QNAT, 23.6 vs 36.8 vs 37.1; $P < .001$; Figure 1A). Indeed, 666 (72%) NOPS extracts had SARS-CoV-2 loads of >1 million copies/mL UTM in the S-gene RT-QNAT (median, 7.2 [interquartile range, 5.8–8.4] $\log_{10}$ copies/mL; Figure 1B). Conversely, the Ct values were significantly higher for discordant results, indicating lower viral loads (Figure 1A). Thus, the Basel SCoV2-S-111bp had an analytical sensitivity and specificity of 99.68% (95% CI, 95%–100%) and 98.99% (95% CI, 91%–100%), respectively. Covering a disease prevalence of 5%–20%, the positive and negative predictive values were 83.9%–96.1% and 99.9%, respectively (Supplementary Table 3). Among the confirmed 930 (12.1%) SARS-CoV-2–positive patients, male sex was more prevalent (49% vs 44%; $P = .002$) and the median age was higher (49 vs 43 years; $P < .001$) compared to those with a negative test result (Table 1). However, higher patient age was not associated with higher SARS-CoV-2 loads (Spearman $r = 0.034$; $P = .30$). Moreover, SARS-CoV-2 was detected in 14 of 354 (4%) children compared with 916 (12%) of the nonpediatric patients ($P < .05$).

To investigate the epidemiology of CARVs and SARS-CoV-2 during the first phase of the pandemic, we identified all NOPS (n = 2394) from patients with influenza-like illness, which had been tested by CARV multiplex NAT between 1 January 2020 (calendar week 1) and 29 March 2020 (calendar week 13). In 942 (39%) cases, at least 1 pathogen had been detected, including 95 with 2 (3.9%) pathogens and 9 with 3 (0.1%) pathogens. The weekly detection for SARS-CoV-2 and CARVs revealed a fluctuating CARV activity until calendar week 7 followed by a steep increase in CARVs, which declined after week 10, when SARS-CoV-2 detection rose sharply (Figure 2A). This was also reflected in the cumulative numbers (Figure 2B; histogram) reaching 48% for SARS-CoV-2 by calendar week 13, followed by rhinovirus (13%) and influenza virus (12%) (Figure 2B; pie chart). Restricting the analysis to 1816 NOPS, from which both CARV multiplex NAT and SARS-CoV-2 RT-QNAT had been requested, SARS-CoV-2 detection was 17% after rhinovirus (22%) and influenza virus (20%) (Figure 2C; pie chart). The weekly detection numbers revealed that SARS-CoV-2 largely replaced all other CARVs except rhinovirus (Figure 2C).

Unlike for SARS-CoV-2, the CARV detection rate was significantly higher in children than in adults ($P < .001$; Table 2). This effect also prevailed when SARS-CoV-2– and CARV-positive cases were analyzed together and when excluding rhinovirus-infected cases from the analysis (Table 2; see also below). Analyzing the age distribution of CARV-positive cases (Figure 3), we found higher detection rates of adenovirus, PIV, RSV, rhinovirus, and influenza virus A/B cases in children ≤16 years of age, while similar rates of HCoV, metapneumovirus, and *M. pneumoniae* were detected in children and adults. Adenovirus-positive patients were significantly younger than patients testing positive for other CARVs or SARS-CoV-2 ($P < .001$; Figure 3, Supplementary Tables 4 and 5). Among adults (1554/1816 [85.5%]), no significant age differences were observed for patients testing positive for any CARV, but patients being positive for SARS-CoV-2 tended to be older than patients testing positive for any other CARV ($P < .01$; Figure 3, Supplementary Table 6).

Among CARV-positive cases, coinfections with 2 or 3 CARVs occurred in 55 (3%) and 5 (0.3%) patients, respectively (Table 3). Rhinovirus and adenovirus as well as rhinovirus and RSV coinfections were almost exclusively found in children ≤2 years of age. In 17 of 1816 (0.9%) patients (15 adults aged 30–93 years and 2 children), SARS-CoV-2 was detected together with at least 1 other CARV, which consisted of a single pathogen in 15 cases—namely, rhinovirus (n = 5), HCoV (n = 5), PIV (n = 3), and influenza virus (n = 2)—and >1 CARV detection in 2 cases (Table 3). Overall, CARV-testing was associated with a high negative predictive value of 98.7% for SARS-CoV-2 infection. The negative predictive value for SARS-CoV-2 infection was higher in CARV-positive children (99.0%; ≤16 years) than in adults (97.1%; >16 years). Conversely, a negative multiplex NAT result after the first detected SARS-CoV-2 case increased the likelihood of SARS-CoV-2 detection from 1% in calendar week 9 to 48% in calendar week 13 (Figure 2).

DISCUSSION

The SARS-CoV-2 pandemic hit Europe in winter 2020, during which a number of circulating CARVs are at their yearly seasonal peak including influenza virus, RSV, PIV, and HCoV. Our analysis from the start to the peak of the pandemic wave of SARS-CoV-2 in northwestern Switzerland has 3 major findings.

First, the early pandemic phase until calendar week 10 was dominated by winter CARVs, emphasizing the importance of

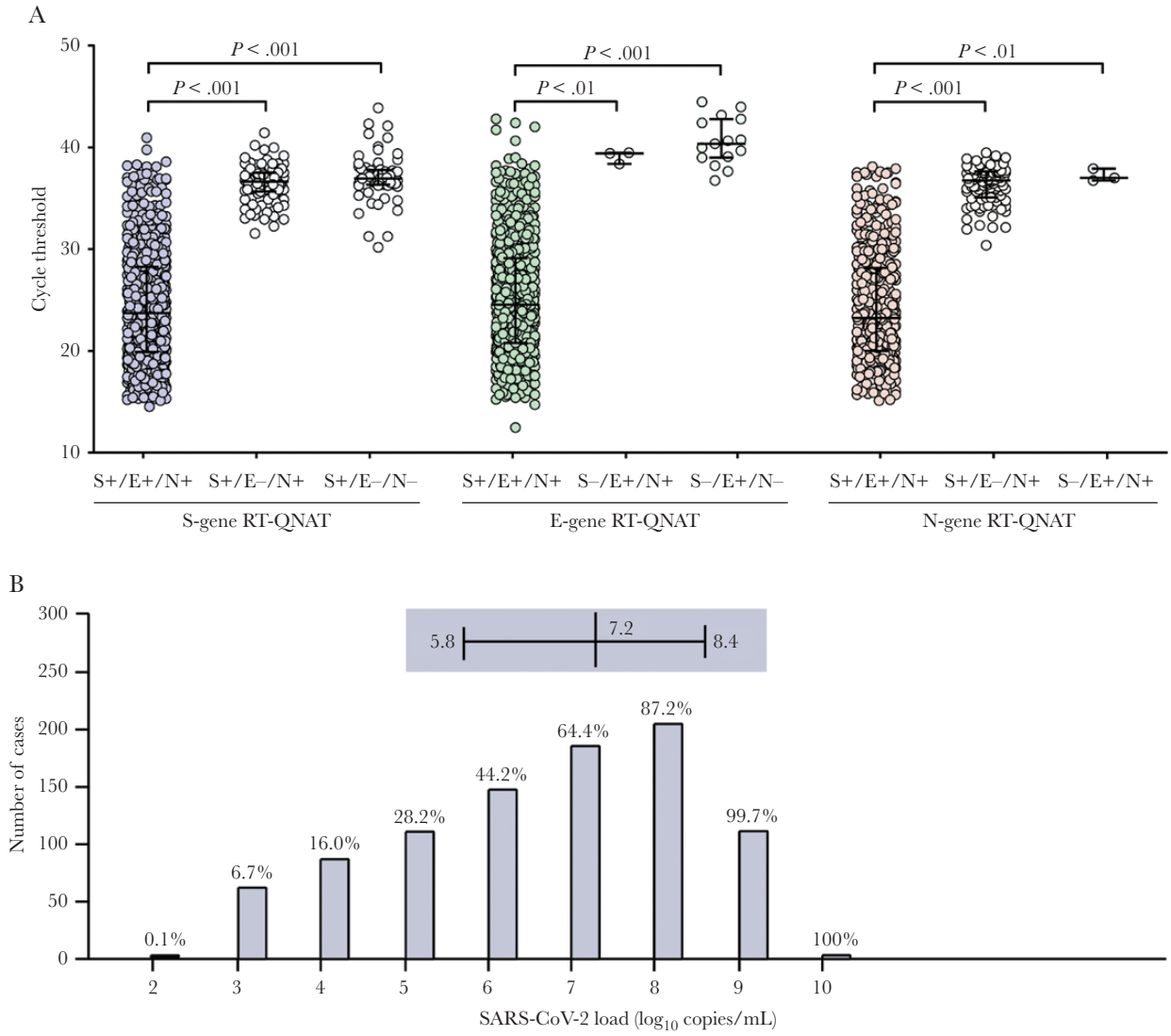

Figure 1. Comparison of cycle thresholds in the S-gene, E-gene, and N-gene reverse-transcription quantitative nucleic acid tests (RT-QNATs) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) loads. Nasopharyngeal/oropharyngeal swabs were submitted for routine testing with the S-gene and E-gene RT-QNATs (n = 7663). Samples with concordant positive or discordant results were subsequently tested with the in-house N-gene RT-QNAT. *A*, Cycling thresholds of concordant positive and discordant samples are displayed (median, 25th and 75th percentiles; n = 7663). *B*, SARS-CoV-2 loads and number of cases determined with the S-gene RT-QNAT in positive samples (median, 25th and 75th percentiles; n = 927).

their rapid and accurate identification due to several reasons: (1) significant morbidity and mortality in vulnerable patients (very young, elderly, immunocompromised) [5]; (2) specific antiviral therapy in case of early influenza A/B detection; (3) appropriate infection control and cohorting strategies upon hospital admission; and (4) prevention of unnecessary empiric antibiotic therapy in CARV-positive patients, or treatment adaptation in case of atypical bacterial agents such as *M. pneumoniae* [10–13]. In this early phase, CARV detection was associated with a high negative predictive value of 98.1% for SARS-CoV-2 infection.

Second, SARS-CoV-2 almost completely replaced the seasonally circulating CARVs within only 3 weeks' time. During calendar weeks 12 and 13, SARS-CoV-2 was practically the only respiratory virus, leading to a total runner-up of 48% when counting all detected CARVs from 1 January 2020. This dynamic evolution was also seen when explicitly analyzing NOPS from patients with respiratory illness for whom both CARV- and SARS-CoV-2 testing had been requested. The weekly detection revealed a significant increase in SARS-CoV-2 infections while the initially increasing CARVs declined. Prepandemic multiplex NAT data from the winter seasons 2010–2015 in our center indicated that winter CARVs such as influenza, RSV, HCoV, and PIV continue to circulate with different peaks until calendar week 25 [5]. These data suggest the intriguing possibility of competing host infections.

Third, diagnosis of SARS-CoV-2 infection was highly reliable, being based on 3 independent molecular tests. Thereby,

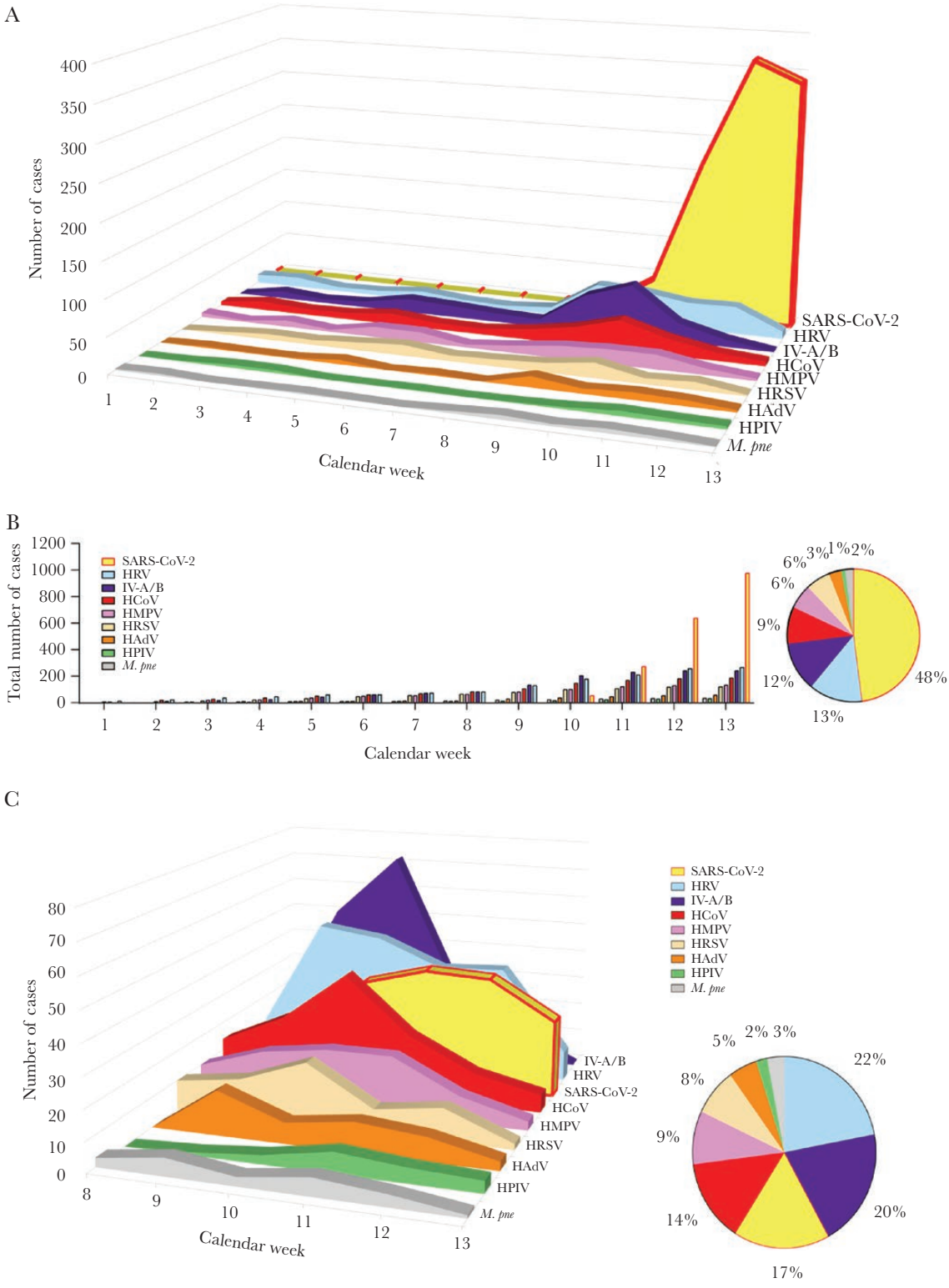

Figure 2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and community-acquired respiratory virus (CARV) epidemiology during the beginning of the epidemic spread from January to March 2020. *A*, Weekly SARS-CoV-2 (n = 8592) and CARV (n = 2394) prevalence in symptomatic children and adults. *B*, Weekly prevalence of cumulated SARS-CoV-2 (n = 8592) and CARV (N = 2394) cases in symptomatic children and adults (bar chart), and cumulated SARS-CoV-2 and CARV cases by calendar week 13 (pie chart). *C*, Weekly SARS-CoV-2 and CARV prevalence in nasopharyngeal/oropharyngeal swabs tested in parallel (n = 1816), and cumulated SARS-CoV-2 and CARV cases by calendar week 13 (pie chart). Abbreviations: HAdV, human adenovirus; HCoV, human coronavirus (229E, OC43, NL63, and HKU1); HMPV, human metapneumovirus; HPIV, human parainfluenza virus (types 1–4); HRSV, human respiratory syncytial virus; HRV, human rhinovirus; IV-A/B, influenza virus A and B; *M. pne*, *Mycoplasma pneumoniae*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Comparison of Severe Acute Respiratory Syndrome Coronavirus 2 and Any Community-Acquired Respiratory Virus Infection in Adults and Children (n = 1816)

Pathogen and Test Result	Age		*P* Value[a]
	≤16 y	>16 y	
SARS-CoV-2			
Positive	5 (2)	143 (9)	<.001
Negative	257 (98)	1411 (91)	
Any CARV[b]			
Positive	166 (63)	479 (31)	<.001
Negative	96 (37)	1075 (69)	
SARS-CoV-2 or any CARV			
Positive	169 (65)	606 (39)	<.001
Negative	93 (35)	948 (61)	
SARS-CoV-2 or CARV[c] (excluding rhinovirus)			
Positive	127 (65)	503 (39)	<.001
Negative	93 (35)	948 (61)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CARV, community-acquired respiratory virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Groups were compared using Mann–Whitney *U* test.

[b]Any CARV includes human adenovirus, human coronavirus (229E, OC43, NL63, and HKU1), influenza virus A and B, human metapneumovirus, human parainfluenza virus (types 1–4), human rhinovirus, human respiratory syncytial virus, and the atypical bacterial agent *Mycoplasma pneumoniae*.

[c]Excluding 145 human rhinovirus–only cases, leaving 1671 cases for analysis.

an independent validation of the WHO-endorsed E-gene was provided. Whereas respiratory panel testing is well validated and widely used in tertiary care centers [5, 14, 15], the response to the SARS-CoV-2 pandemic hinges on the performance of a new diagnostic test for a new viral agent, and its communication within a short turnaround time. To accomplish this task, we prospectively tested all NOPS directly in parallel with the commercial Roche E-gene and our Basel S-gene RT-QNAT. This outstanding opportunity for independent test validation on >7600 patients demonstrated high concordance of 97.5% between both assays including 825 (11%) SARS-CoV-2 infections, which could be communicated without further delay to the treating physicians. Importantly, comparison of the Ct values revealed that the discordance mostly resulted from SARS-CoV-2 loads at the limit of detection. Thus, discordant results became increasingly likely at very low, hence limiting viral loads in the NOPS, most likely reflecting a stochastic distribution of genomes in the analyte.

A limitation of our study is the dependence on the preanalytic steps of NOPS sampling, especially in the light of the natural course of SARS-CoV-2 infection. We addressed this challenge through repeated instructions and video clips demonstrating the correct use of personal protective equipment, validated swab sets, defined sampling procedures in dedicated hospital areas, and direct laboratory processing. In case of lower respiratory tract infectious diseases, viral loads in the upper respiratory tract may decrease, and testing of endotracheal aspirates or bronchoalveolar lavage fluid is advisable [5, 16–19]. While the time of exposure and symptom onset was not available to us, our study investigated only the first diagnostic testing in NOPS, which was obtained in 90% of cases in the primary care or outpatient departments (Table 1). This suggests that most patients did not require immediate hospitalization, which has been described to typically occur 1 week after symptom onset [20], similar to patients with influenza-like illness seeking medical outpatient care [5, 21]. Early testing is clinically and epidemiologically advisable in view of high viral loads detectable in exposed asymptomatic/presymptomatic and oligosymptomatic persons [16, 22].

Since our diagnostic laboratory is serving both regional tertiary care centers for adults and children, we examined the age distribution of SARS-CoV-2 and CARV infection. Indeed,

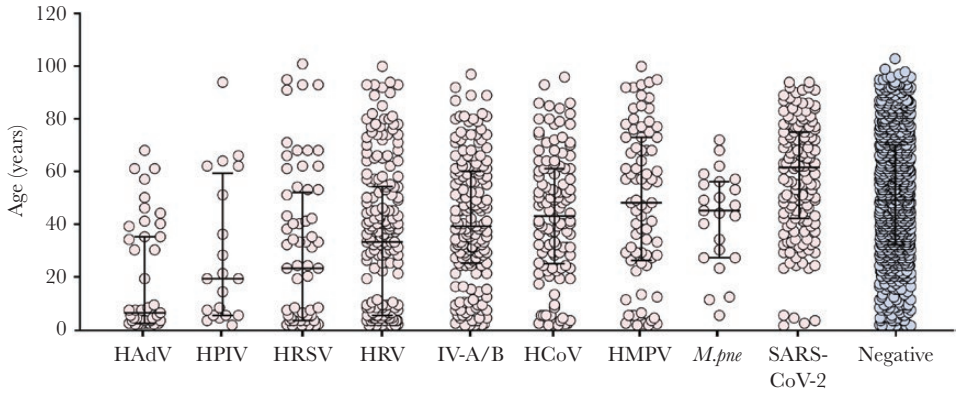

Figure 3. Age distribution of patients positive for community-acquired respiratory virus (CARV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Nasopharyngeal/oropharyngeal swabs were analyzed in parallel for different CARVs with multiplex nucleic acid test and SARS-CoV-2 with reverse-transcription quantitative nucleic acid test. Patient age of CARV- or SARS-CoV-2–positive patients is displayed (median, 25th and 75th percentiles; n = 1816), and compared using Mann–Whitney *U* test (Table 3; Supplementary Tables 4–6). Abbreviations: HAdV, human adenovirus; HCoV, human coronavirus (229E, OC43, NL63, and HKU1); HMPV, human metapneumovirus; HPIV, human parainfluenza virus (types 1–4); HRSV, human respiratory syncytial virus; HRV, human rhinovirus; IV-A/B, influenza virus A and B; *M. pne*, *Mycoplasma pneumoniae*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Patients With >1 Positive Severe Acute Respiratory Syndrome Coronavirus 2 or Community-Acquired Respiratory Virus Detection (n = 1816)

CARVs Detected	No. of Patients	Age ≤2 y	Age ≤5 y	Age ≤16 y	Age >16 y
SARS-CoV-2 and HCoV	5	…	…	…	5
SARS-CoV-2 and HRV	5	…	1	1	4
SARS-CoV-2 and HPIV	3	…	…	…	3
SARS-CoV-2 and IV-A	2	…	…	…	2
SARS-CoV-2, HRV, and HAdV	1	…	…	…	1
SARS-CoV-2, HRV, HRSV, and HPIV	1	…	1	1	…
HRV and HAdV	11	8	10	10	1
HRV and HCoV	6	2	2	3	3
HRV and IV-A/B	5	1	1	2	3
HRV and HRSV	5	3	4	4	1
HRV and HPIV	3	…	2	2	1
HRV and HMPV	2	1	1	1	1
HRV and *Mycoplasma pneumoniae*	1	…	…	…	1
HRV and *Bordetella parapertussis*	1	…	1	1	…
HRV, HCoV, and IV-A/B	1	…	…	1	…
HRV, HCoV, and HAdV	1	…	1	1	…
HRV, HRSV, and IV-A/B	1	…	1	1	…
HRV, HPIV, and HAdV	1	…	…	1	…
HCoV and IV-A/B	3	…	…	…	3
HCoV and HRSV	3	2	2	2	1
HCoV and HPIV	2	…	…	…	2
HCoV and HMPV	2	1	1	1	1
HCoV and HAdV	2	1	2	2	…
HCoV, HMPV, and *M. pneumoniae*	1	…	1	1	…
HAdV and HRSV	2	…	1	1	1
HAdV and IV-A/B	1	…	…	…	1
HAdV and *B. parapertussis*	1	…	…	1	…
HAdV and *M. pneumoniae*	1	…	…	…	1
HAdV and HMPV	1	1	1	1	…
IV-A/B and HRSV	2	1	1	2	…
IV-A/B and HMPV	1	…	…	…	1
Total	77	21	34	40	37

Abbreviations: HAdV, human adenovirus; HCoV, human coronavirus (229E, OC43, NL63, and HKU1); HMPV, human metapneumovirus; HPIV, human parainfluenza virus (types 1–4); HRSV, human respiratory syncytial virus; HRV, human rhinovirus; IV-A/B, influenza virus A and B; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

patients testing positive for adenovirus and RSV were significantly younger and more likely to be children <5 years of age, among whom SARS-CoV-2 infection remained rare, in line with other studies [20, 23]. Although SARS-CoV-2–positive adults were older than patients testing positive for CARVs, the median age of >40 years in CARV-positive patients suggests that similar adult populations were at risk for established CARVs or for the novel SARS-CoV-2.

Our study provides intriguing observations regarding the epidemiology of SARS-CoV-2 in its capacity to replace circulating CARVs among adults. Comprehensive data from our center from 2010–2015 indicate that winter CARVs such as influenza, RSV, metapneumovirus, HCoV, and PIV co-circulate with different peaks until calendar week 25, thus 10 weeks longer than in the current SARS-CoV-2 pandemic year of 2020 [5, 24]. Notably, coinfection rates of CARVs with SARS-CoV-2 were rather low as reported here and by others [8], suggesting a competitive infection situation. Although we cannot exclude that SARS-CoV-2 is simply filling the void, these data suggest the possibility of competing viral host infections.

It is presently unclear whether virus properties such as higher infectiousness, facilitated transmission, or increased host susceptibility are the decisive factors conferring significant advantages to SARS-CoV-2 in this first wave of the pandemic. Regarding the infectiousness of SARS-CoV-2, our data provide independent evidence for very high viral loads in the order of 1–100 million copies/mL of transport medium. Even if these high numbers only carry 1000-fold lower infectious units, the infectious activity remains high in the patients' respiratory secretions [25]. Notably, similarly high viral loads have also been described for CARVs including influenza or RSV [5, 26–28]. Regarding transmission, SARS-CoV-2 is thought to behave less like influenza viruses spreading significantly by aerosols [29, 30], but rather like RSV spreading by droplets, contaminated surfaces, and hands [31, 32]. However, aerosolization of SARS-CoV-2 may also play a role, especially when associated with

high-velocity airstreams during sneezing, singing, and medical procedures [33–35].

Finally, increased susceptibility of the human host to infection by this novel, presumably zoonotic coronavirus remains as a presently difficult-to-estimate factor. Already the first reports from China in January 2020 indicated that SARS-CoV-2 is well adapted to the human host [36]. Unlike the first severe acute respiratory syndrome coronavirus, SARS-CoV-2 is easily transmitted from human-to-human before the start of symptoms, hence facilitating the pandemic spread [22, 37, 38]. However, SARS-CoV-2 seems to be susceptible to type 1 interferons [39], and induces cytokines including interleukin 6 [40] through excessive macrophage activation upon progression to viral pneumonia [41].

What could be the underlying mechanisms for an increased susceptibility to SARS-CoV-2 infection competitively replacing established CARVs in a mostly adult population? Hand washing, social distancing, and lockdown measures would be predicted to affect CARVs and SARS-CoV-2 alike, but were not yet sufficiently effective to prevent the upswing of the pandemic wave.

We hypothesize that the decisive factors may be the differential net response of the host to virus-induced unspecific innate immunity on the one hand and to virus-specific adaptive immune memory on the other hand. CARV infections are known to cause an innate immune response including type 1 interferons, which reduces the risk of coinfection by other viruses including SARS-CoV-2 [24, 42]. Since adults have been repeatedly exposed to CARVs in the past, their CARV-specific immune memory may not be high enough to prevent symptomatic CARV reinfection, but is readily boosted upon reexposure, hence limiting CARV replication and the associated inflammation elicited by innate immunity as reviewed [5]. We propose that thereby the semi-immune mostly adult host population becomes available for SARS-CoV-2 infection. Since SARS-CoV-2 is novel and thus having little, if any, specific immune memory, its replication is prolonged, evoking pronounced inflammation, delaying infection by other circulating CARVs, extending transmission periods, and shifting the epidemiologic curve in favor of this novel agent. This differential net response of virus-induced unspecific innate immunity and virus-specific adaptive immune memory may also contribute to the puzzling lower infection rates seen in small children, who typically replicate CARVs in high frequency and high levels over extended periods, hence interfering with SARS-CoV-2. However, CARVs may differ in their propensity to interfere and may be low for rhinovirus. Indeed, 46 of 77 coinfections (60%) involved rhinovirus. Although other (co-)factors cannot be excluded such as exposure in the environment and hospitals as well as age-dependent changes in (co-)receptor and immune function [43], our hypothesis will be testable by analyzing whether or not vaccines to CARVs and/or to SARS-CoV-2 change this competitive epidemiologic risk [44]. It is possible that CARV interference will be reduced during the summer months, putting younger age populations at risk for the pandemic SARS-CoV-2. Although influenza vaccination may potentially increase the opportunity for infections with other CARVs and SARS-CoV-2, the presumed time gained from being protected through innate immune interference would be <3 weeks. Thus, protection from influenza through vaccination remains an important public health objective given the short window for effective antiviral treatment within <48 hours after symptom start [21].

In conclusion, circulating CARVs were dominant during the first phase of the COVID-19 pandemic, but rapidly replaced within 2 weeks by SARS-CoV-2. A comprehensive testing strategy covering SARS-CoV-2 and CARVs is central to infection control and clinical management. Epidemiologic determinants of the competitive infection risk between established CARVs and the novel SARS-CoV-2 require further research, including studies of unspecific innate immune interference and virus-specific adaptive immune memory.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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