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Resurgence of common respiratory viruses in patients with community-acquired pneumonia (CAP)—A prospective multicenter study

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ABSTRACT

Background: Community-acquired pneumonia (CAP) is a major global cause of death and hospitalization. Bacteria or community-acquired viruses (CARVs) cause CAP. COVID-19 associated restrictions effectively reduced the circulation of CARVs.
Objectives: The aim of this study was to analyze the proportion of CARVs in adult patients with CAP from mid-2020 to mid-2023. Specifically, we aimed to compare the rate of influenza virus, SARS-CoV-2, and RSV detections in patients aged 18–59 years and ≥60 years.
Study design: We analyze the proportion of 21 community-acquired respiratory viruses (CARVs) and three atypical bacteria (*Bordetella pertussis, Legionella pneumophila*, and *Mycoplasma pneumoniae*) in nasopharyngeal swab samples using molecular multiplex methods within the prospective, multicentre, multinational study of the German study Group CAPNETZ. We used stringent inclusion criteria throughout the study.
Results: We identified CARVs in 364/1,388 (26.2 %) patients. In detail, we detected SARS-CoV-2 in 210/1,388 (15.1 %), rhino-/enterovirus in 64/1,388 (4.6 %), influenza virus in 23/1,388 (1.6 %) and RSV in 17/1,388 (1.2 %) of all patients. We detected RSV and influenza more frequently in patients ≥60 years, especially in 22/23 compared to the previous season. None of the atypical bacteria were detected.
Conclusions: Beginning in 2023, we demonstrate a re-emergence of CARVs in CAP patients. Effective vaccines or specific antiviral therapies for more than two thirds of the detected viral infections are currently available. High detection rates of vaccine-preventable viruses in older age groups support targeted vaccination campaigns.

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1. Background

Community-acquired pneumonia (CAP) poses a significant global health burden [1]. While often linked to bacteria, recent studies have highlighted the etiologic importance of viruses [2]. This became particularly evident during the COVID-19 pandemic [3,4]. Our earlier research indicated that COVID-19 associated restrictions effectively reduced the circulation of community-acquired respiratory viruses (CARVs) like influenza virus and RSV [3]. With specific antivirals, monoclonal antibodies, and vaccines available, understanding the epidemiology of CARVs is crucial for individual healthcare and public health. We hypothesize that after the relaxation of COVID-19 restrictions, seasonal CARVs like influenza virus and RSV may resurface. However, the epidemiological characteristics and reasons for the resurgence of CARVs in patients with CAP remain unclear.

2. Objectives

We aimed to analyze the proportion of CARVs in adult patients with CAP from mid-2020 to mid-2023. Specifically, we aimed to compare the rate of influenza virus, SARS-CoV-2, and RSV detections in patients aged 18–59 years and ≥60 years.

3. Study design

3.1. Study design and patients

We analyzed respiratory pathogen frequencies over three consecutive years (July 2020 - May 2023) using the prospective, multinational, multicentre cohort of CAPNETZ (Competence Network for CAP). Inclusion criteria were age ≥18 years, a new lung opacification on chest radiograph, and at least one of the following clinical findings: cough, purulent sputum, fever (≥38.3 °C), or focal chest sign on auscultation. We excluded anyone recently hospitalized, with severe immune problems, or active tuberculosis. Each patient provided a nasopharyngeal swab sample in universal transport medium (UTM). Each study center submitted the study samples to the central testing facility in Freiburg, Germany, where all molecular testing of study samples was done immediately upon receipt.

3.2. Laboratory testing

We used the commercial multiplex PCR FTD Respiratory Pathogens 21 Assay (Siemens Healthineers, Eschborn, Germany) according to the manufacturer's recommendation. This included testing for adenovirus, coronavirus (CoV) 229E, CoV OC43, CoV NL63, CoV HKU1, SARS-CoV-2, human bocavirus, human metapneumovirus (HMPV), human rhinovirus/enterovirus, influenza virus $A + B$, parainfluenzavirus 1–4, respiratory syncytial virus (RSV) $A + B$. We complemented testing by in-house PCR for the atypical bacteria *Bordetella pertussis, Legionella pneumophila*, and *Mycoplasma pneumoniae* [3].

3.3. Ethics

We obtained signed informed consent from every single individual for prospective bio banking. Institutional Review Board (IRB) of each participating clinical center was obtained. A central IRB approval is available by the Ethics Committee of the Hannover Medical School; project approval number: 301–2008.

3.4. Data analysis

We conducted descriptive and analytic statistics using GraphPad Prism Version 9.5.1.733 (GraphPad Software, LLC). For pathogen diversity we used the Shapiro-Wilk test for small n to test for normality and non-parametric Mann-Whitney test.

4. Results

We studied 1388 CAP patients in total (421 in 2020/21, 360 in 2021/22, 607 in 2022/23). The median age was 68 years (range 18–99), with 38.1 % females (Table 1). We detected CARVs in 364/1388 (26.2 %) of patients. Specifically, SARS-CoV-2 was detected at a rate of 15.1 % (210 cases), rhino-/enterovirus at 4.6 % (64 cases), influenza virus at 1.6 % (23 cases), RSV at 1.2 % (17 cases), parainfluenza virus at 1.2 % (17 cases), and seasonal coronavirus at 1.2 % (17 cases). Of all viral infections, 40/364 (10.9 %) were vaccine preventable, excluding SARS-CoV-2. We did not detect atypical bacteria. Pneumonia-related mortality rate was 9.9 % (76/1388) including two patients under the age of 60 years.

In 2020/21, the most frequently detected pathogens were SARS-CoV-2 in 93/421 (22.1 %) of cases, rhino-/enterovirus in 17/421 (4.3 %), and non-SARS-CoV-2 CoV in 4/421 (1.0 %). We identified no case of RSV or influenza virus. In 2021/22, we detected SARS-CoV-2 in 52/360 (14.4 %), followed by rhino-/enterovirus in 16/360 (4.4 %), CoV (OC 43, HKU 1, NL 63) and influenza virus A in 5/360 each (1.4 %). In 2022/23, SARS-CoV-2 accounted for 65/607 (10.7 %) positive findings, rhino-/enterovirus for 31/607 (5.1 %), influenza virus (including the only influenza B case) for 16/607 (2.6 %), and RSV for 13/607 (2.1 %).

We analyzed monthly detection rates, which ranged from 0 % to 48.7 % (Fig. 1). Each month, we found a median of 1.5 viral species in 2020/21, 3 in 2021/22, and 4.5 in 2022/23. Comparing detection rates of the post-pandemic months of 2023 with pandemic months (July 2020 to December 2022), a significant difference was found (Mann-Whitney test, $p < 0.0001$), with a median of two pathogens during the pandemic versus six in the post-pandemic phase.

Finally, we compared SARS-CoV-2, influenza virus, RSV, and rhino-/enterovirus detection rates between winter seasons 21/22 and 22/23. Influenza virus and RSV detections increased in the second season, while SARS-CoV-2 detections declined. Rhino-/enterovirus detections remained unchanged (Table 2, Fig. 2). Notably, we detected RSV and influenza were more frequently in patients ≥60 years, especially in 22/23 compared to the previous season (Fig. 3, Table 3).

5. Discussion

Our study confirms the hypothesis of a resurgence of seasonal CARVs. We demonstrated the transition from CARVs to SARS-CoV-2 in 2020 in our previous study with the CAPNetz cohort [3]. However, there were concerns about an out-of-season resurgence of CARVs [5]. We detected an unexpected rise of RSV infections in adults as early as October 2022, which is a matter of concern. Systematic surveillance in children has shown a massive surge of RSV cases in the Northern hemisphere by the end of 2022. A lack of exposure due the COVID-19 associated prevention measures in combination with waning immunity might have increased the pool of susceptible children [6]. Since children serve as primary source of infection in adults increased spill over infections into the elderly population seem plausible. Importantly, the disease burden of RSV in adults is underappreciated and highlights the importance of diagnostics for i). optimal patient care ii). infection control and iii). public health. Similarly, we noticed a significant decline of influenza during the first phase of the COVID-19 pandemic [3]. A lack of

Table 1
Baseline demographic characteristic of all enrolled cases and in each season.

Characteristic	All enrolled cases, n = 1388	Cases in season 2020/21, n = 421	Cases in season 2021/22, n = 360	Cases in season 2022/23, n = 607
Median age, years (95 % confidence interval)	68 (67 – 70)	66 (64 – 68)	68 (66 –70)	71 (69 – 72)
Sex,% female	38.1 %	36.2 %	38.1 %	39.2 %

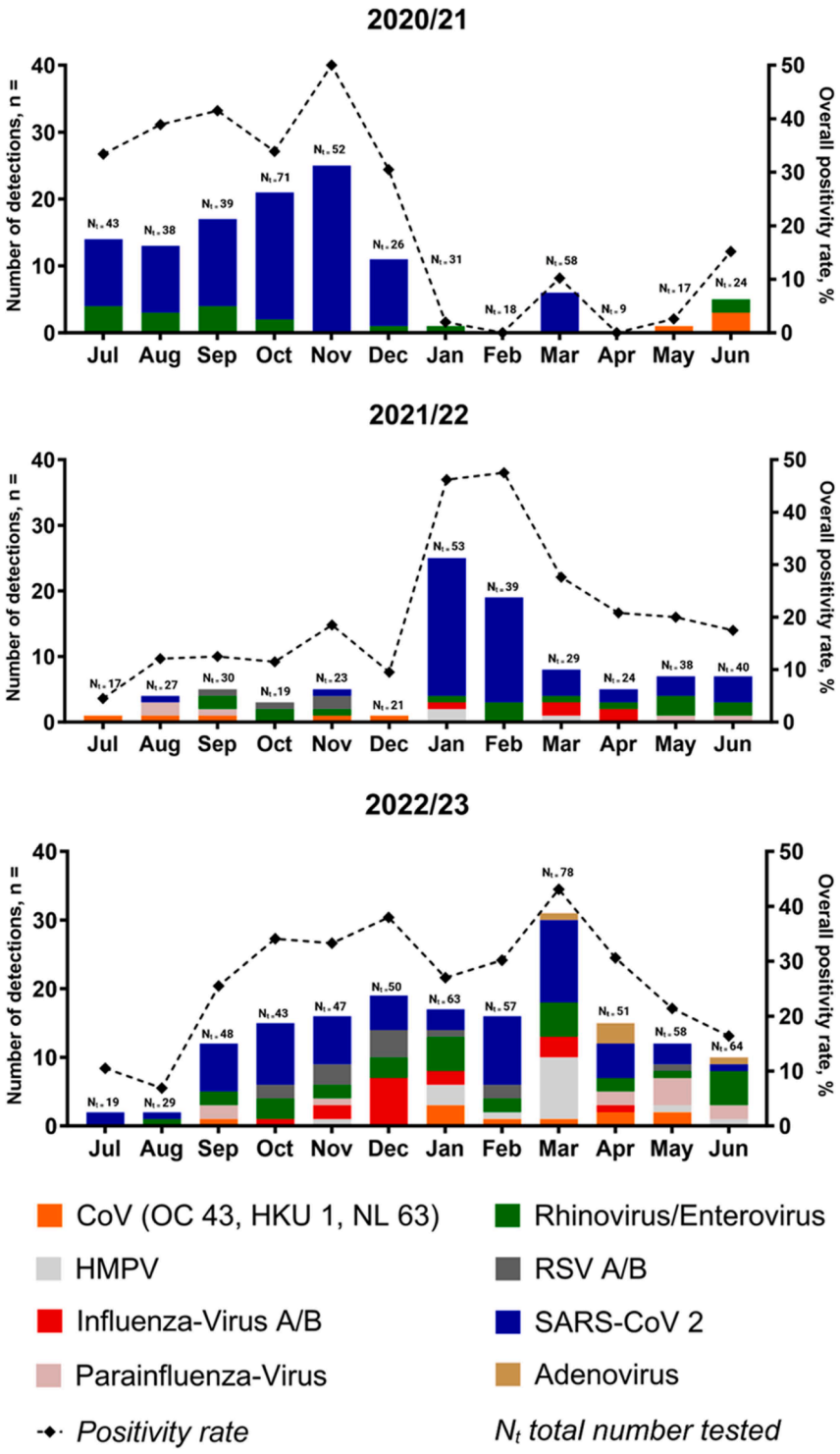

Fig. 1. Monthly detection rates of viral respiratory pathogens in CAP-cases in three consecutive 12-month intervals.

neutralizing antibodies against influenza in adults underscores the importance of targeted influenza and RSV vaccination campaigns [7]. Therefore, it is instrumental to better understanding the epidemiology of CARVs [2]. For individual health, early case detection might optimize antibiotic stewardship [8,9]. A growing number of respiratory viral infections are now treatable with specific drugs/monoclonal antibodies or are vaccine preventable. Further, CARVs are relevant pathogens of hospital-acquired pneumonia and respective outbreaks have been described [10]. Thus, early detection on admission can decrease intra-hospital spread and guide infection control to prevent nosocomial transmission.

Interestingly, we did not detect *Mycoplasma pneumoniae* in our cohort, which is in line with other reports [11]. The reasons for this slow re-emergence are unclear but a viral-bacterial interference between SARS-CoV-2 and *Mycoplasma pneumoniae* might play a role [11].

Lastly, we found a mortality rate of 9.9 %, which differs from the 16.8 % reported in Germany in 2022 [12]. We did not include immunosuppressed patients in our study, which might explain the lower mortality rate.

Strength of our study include strict inclusion criteria for CAP patients

Table 2
Detection rates of SARS-CoV-2, influenza virus, RSV, and rhino-/enterovirus in all patients recruited from Sep-May 21/22 compared to Sep-May 22/23.

Season	SARS-CoV-2, n=	Influenza virus, *n*=	RSV, *n*=	Rhino-/ enterovirus, *n*=
Sep-May 21/22 (*n* = 276)	45 (16.3 %)	5 (1.8 %)	3 (1.1 %)	14 (5.1 %)
Sep-May 22/23 (*n* = 495)	63 (12.7 %)	18 (3.6 %)	14 (2.8 %)	26 (5.3 %)
Total (*n* = 771)	108 (14 %)	23	17	40

from multiple centers for three years, which remained unchanged and the consistent use of the same molecular testing method. A key limitation was not using lower respiratory samples, which might have missed some viral infections. However, recent studies show over 80 % positive agreement between nasopharyngeal swabs and deeper lung samples [13]. Our study clearly shows the re-emergence of CARVs in patients with CAP and underscores the role of swift diagnostic testing for patient management and public health.

CAPNETZ was founded by a BMBF grant (FKZ 01KI07145) 2001–2011. Associated member of German Center for Lung Research (FKZ 82DZL002B4) since 2013.

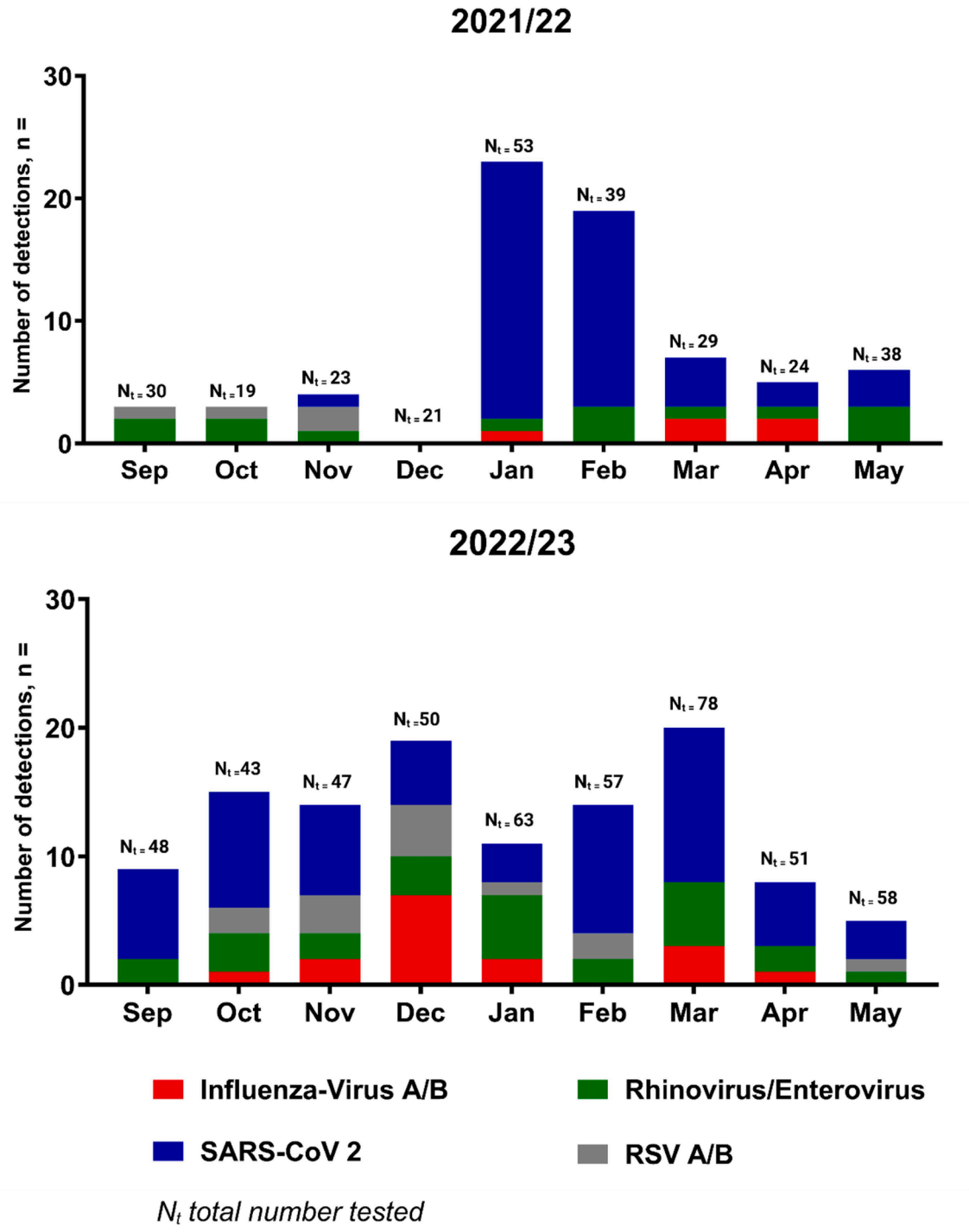

Fig. 2. Number of detections of SARS-CoV-2, influenza virus, RSV, and rhino-/enterovirus in patients recruited from Sep-May 21/22 and Sep-May 22/23. Number above each column indicates total number of cases enrolled per month.

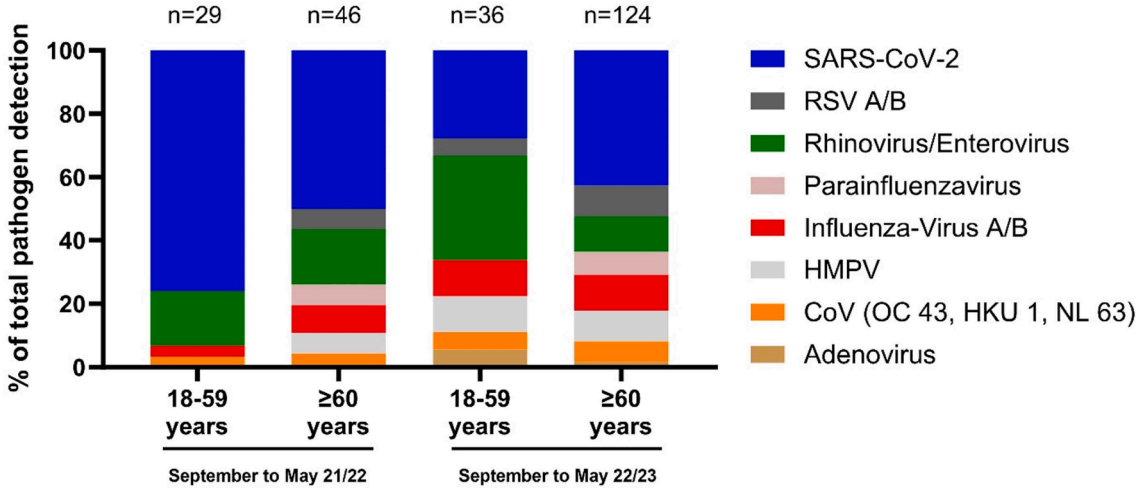

Fig. 3. Proportion of viral pathogens detected in patients 18–59 years and ≥60 years of age.

Table 3
Detection rates of SARS-CoV-2, influenza virus, RSV, and rhino-/enterovirus in different age groups recruited from Sep-May 21/22 and Sep-May 22/23.

Age, years	SARS-CoV-2, *n*= (% of all tested in age group)	Influenza virus, *n*= (% of all tested in age group)	RSV, *n*= (% of all tested in age group)	Rhino-/enterovirus, *n*= (% of all tested in age group)
18–59 (*n* = 221)	32 (14.5 %)	5 (2.3 %)	2 (0.9 %)	17 (7.7 %)
≥60 (*n* = 550)	76 (13.8 %)	18 (3.3 %)	15 (2.7 %)	23 (4.2 %)
Total (*n* = 771)	108 (14 %)	23 (3 %)	17 (2.2 %)	40 (5.2 %)

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Disclaimer

The study was carried out following definitions of Good Clinical Practice, according to the declaration of Helsinki. We obtained signed informed consent for prospective bio banking from every single individual. Institutional Review Board (IRB) of each participating clinical center was obtained. A central IRB approval is available by the Ethics Committee of the Hannover Medical School; project approval number: 301–2008.

CRediT authorship contribution statement

Theo Dähne: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Wolfgang Bauer:** Writing – review & editing, Investigation. **Andreas Essig:** Writing – review & editing, Investigation. **Bernhard Schaaf:** Writing – review & editing, Investigation. **Grit Barten-Neiner:** Project administration, Methodology, Data curation. **Christoph D. Spinner:** . **Mathias W. Pletz:** . **Gernot Rohde:** Writing – review & editing, Methodology, Investigation. **Jan Rupp:** Writing – review & editing, Methodology, Investigation. **Martin Witzenrath:** Writing – review & editing, Methodology, Investigation. **Marcus Panning:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

All authors have no conflict of interest to declare.

Appendix

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