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LETTER TO THE EDITOR

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Coinfections with SARS-CoV-2 and other respiratory viruses in Southeastern France: A matter of sampling time

To the Editor,

We read with interest the article by Nowak et al.[1] Coinfections with several respiratory viruses are common worldwide and can represent up to 42% of infections with non-SARS-CoV-2, endemic coronaviruses.[2] However, the relative risk of coinfections is mainly based on the coincidence of the seasonality of these viruses. Regarding SARS-CoV-2, its codetection with other respiratory viruses has been reported with frequencies that varied from less than 5%[1,3–5] to 27%.[6] Such variations could be explained partially by differences in the incidence of viral respiratory infections that varies considerably according to the study period, the geographical area, and the age group. The frequency of these coinfections and the viruses they involved deserve further studies at multiple regional scales as this can have consequences on the diagnosis strategies and the patients' clinical management.

At the University Hospital Institute Méditerranée Infection in Marseille, Southeastern France, we implemented the SARS-CoV-2 diagnosis by reverse-transcription polymerase chain reaction (PCR) since the end of January 2020.[7] Between March 1 and April 30, 2020, 38,633 patients from all four university hospitals of Marseille were tested by PCR for SARS-CoV-2 and 4,975 (12.9%) resulted positive (https://www.mediterranee-infection.com/covid-19/). During the same period of time, respiratory samples from 4,797 patients were tested for non-SARS-CoV-2 respiratory viruses and 28% of the patients (n = 1,358) were positive for one or more tested viruses.

A total of 4,222 patients were tested during the 2-month period for SARS-CoV-2 and other respiratory viruses as well. Among them, 643 (15.2%) were diagnosed with SARS-CoV-2, 1,095 (25.9%) were diagnosed with one or more non-SARS-CoV-2 respiratory viruses, and 27 (0.6% of the 4,222 patients and 4.2% of those SARS-CoV-2-positive) were coinfected with SARS-CoV-2 and another respiratory virus, mostly rhinoviruses (n = 11), endemic coronaviruses (n = 5), and influenza A or B viruses (n = 4) (Table 1).

Interestingly, the circulation of SARS-CoV-2 was low until mid-March (85 cases between March 1 and March 18) and high from mid-March until mid-April (558 cases between March 19 and April 15) (Figure 1). Conversely, the circulation of other respiratory viruses was high until mid-March (938 cases between March 1 and March 18) and very low thereafter (130 cases, including 57 cases in April). The number of infections with non-SARS-CoV-2 respiratory viruses dropped by 17.7 times, from 1,011 to 57, between March and April, and the number of coinfections with SARS-CoV-2 and other respiratory viruses consequently decreased by 3.5 times, from 21 to 6, between these 2 months. Therefore, the chance to detect coinfections with SARS-CoV-2 and another virus was small in Marseille during the period of the study.

The 27 patients infected with SARS-CoV-2 and another respiratory virus comprised 13 men (48.2%) and their mean age (±standard deviation) was 59.6 ± 23.8 years. Similar characteristics were observed for patients studied by Nowak et al.[1] who reported 44% of men and a mean age of ≈60 years among SARS-CoV-2-positive patients positive for another respiratory virus. In our cohort, patients positive for SARS-CoV-2 were significantly more likely to be men (57.8%) and older (mean age of 61.3 ± 20.1 years) compared to patients infected with viruses other than SARS-CoV-2 (49.8% male with a mean age of 29.2 ± 27.7 years).

Our findings that involved the largest cohort of patients, to our knowledge, tested for SARS-CoV-2 and other respiratory viruses show that coinfections are possible, but their occurrence requires a coincidence of their epidemic periods. This justifies using a syndromic diagnostic strategy, primarily through the use of multiplex PCR assays, as we and others have implemented in clinical microbiology and virology laboratories.[7–9] Nonetheless, the frequency of coinfections, which make it difficult to estimate the clinical impact of each respiratory virus, largely depends on the rate of coincidence of these viruses. Since its emergence in December 2019, SARS-CoV-2 has shown different incidence patterns according to the geographical area and the time of sampling, and the overlap between its temporal distribution and that of other respiratory viruses, therefore, varied considerably. In the coming winter and spring seasons, it is a possibility that epidemics of common respiratory viruses, including influenza viruses, will overlap with epidemics of SARS-CoV-2, and accurate and timely diagnosis will be important. Currently, the outcome of the SARS-CoV-2 pandemic remains uncertain, but previous findings warrant adding the detection of this new virus in syndromic approaches on the assumption that this new coronavirus might circulate in the future in a seasonal manner like the other respiratory viruses, particularly like endemic human coronaviruses.

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TABLE 1 Epidemiological and virological features of SARS-CoV-2-negative and -positive patients coinfected with other respiratory viruses using the FTD Respiratory pathogens 21 (Fast Track Diagnosis, Luxembourg), the Biofire FilmArray Respiratory panel 2 plus (Biomérieux, Marcy-l'Etoile, France), the Respiratory Multi-Well System r-gene (Argene, BioMérieux), or the GeneXpert Xpert Flu/RSV (Cepheid, Sunnyvale, CA) assays

Epidemiological features and viruses	All patients (*N* = 1,711)	(1) SARS-CoV-2-negative but positive for another respiratory virus (*N* = 1,068)	(2) SARS-CoV-2 positive (*N* = 643)	(3) SARS-CoV-2-positive without coinfection (*N* = 616)	(4) SARS-CoV-2-positive with coinfection (*N* = 27)	*p* Value[a]	*p* Value[b]	*p* Value[c]
Age, mean ± standard deviation (years)	41.3 ± 29.5	29.2 ± 27.7	61.3 ± 20.1	61.4 ± 20.0	59.6 ± 23.8	**$<2 \times 10^{-16}$**	**$<2 \times 10^{-16}$**	.7103
Gender, *n* (%)								
Male	904 (52.8%)	532 (49.8%)	372 (57.8%)	359 (58.3%)	13 (48.2%)	**.001251**	**.003**	.2967
Female	807 (47.2%)	536 (50.2%)	271 (42.2%)	257 (41.7%)	14 (51.8%)			
Influenza viruses, *n* (%)								
Influenza A virus	212 (12.4%)	210 (19.7%)	2 (0.3%)	-	2 (7.4%)			
Influenza B virus	235 (13.7%)	233 (21.8%)	2 (0.3%)	-	2 (7.4%)			
Parainfluenza viruses, *n* (%)								
Parainfluenza virus 1	3 (0.2%)	3 (0.3%)	0 (0%)	-	0 (0%)			
Parainfluenza virus 2	9 (0.5%)	8 (0.8%)	1 (0.2%)	-	1 (3.7%)			
Parainfluenza virus 3	8 (0.5%)	8 (0.8%)	0 (0%)	-	0 (0%)			
Parainfluenza virus 4	12 (0.7%)	10 (0.9%)	2 (0.3%)	-	2 (7.4%)			
Human endemic coronaviruses, *n* (%)								
Coronavirus 229E	34 (2.0%)	33 (3.1%)	1 (0.2%)	-	1 (3.7%)			
Coronavirus OC43	44 (2.6%)	42 (3.9%)	2 (0.3%)	-	2 (7.4%)			
Coronavirus NL63	61 (3.6%)	61 (5.7%)	0 (0%)	-	0 (0%)			
Coronavirus HKU1	66 (3.9%)	64 (6.0%)	2 (0.3%)	-	2 (7.4%)			
Respiratory syncytial virus	22 (1.3%)	22 (2.1%)	0 (0%)	-	0 (0%)			
Bocavirus	67 (3.9%)	65 (6.1%)	2 (0.3%)	-	2 (7.4%)			
Adenovirus	85 (5.0%)	84 (7.9%)	1 (0.2%)	-	1 (3.7%)			
Metapneumovirus	65 (3.8%)	64 (6.0%)	1 (0.2%)	-	1 (3.7%)			
Rhinovirus	335 (19.6%)	324 (30.4%)	11 (1.7%)	-	11 (40.7%)			
Enterovirus	38 (2.2%)	36 (3.4%)	2 (0.3%)	-	2 (7%)			

Note: $\chi 2$ or Fisher exact test were used to compare differences between proportions. Quantitative data means were compared using the one-way analysis of variance or Student's test. Significant *p* values are in bold font.

[a]Comparison of SARS-CoV-2-negative (1) versus SARS-CoV-2-positive (2).

[b]Comparison of SARS-CoV-2-negative (1) versus SARS-CoV-2 positive without coinfection (3) versus SARS-CoV-2 positive with co-infection (4).

[c]Comparison of SARS-CoV-2-positive without coinfection (3) versus SARS-CoV-2-positive with coinfection (4).

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: Philippe Colson, Philippe Gautret, Bernard La Scola, Didier Raoult. Contributed materials/analysis tools: Céline Boschi, Van Thuan Hoang, Audrey Giraud-Gatineau, Laetitia Ninove, Jean-Christophe Lagier, Philippe Gautret, Philippe Colson. Analyzed the data: Céline Boschi, Van Thuan Hoang, Bernard La Scola, Philippe Gautret, Didier Raoult, Philippe Colson. Wrote the paper: Céline Boschi, Philippe Gautret, Didier Raoult, Philippe Colson. All authors approved the last version of the manuscript.

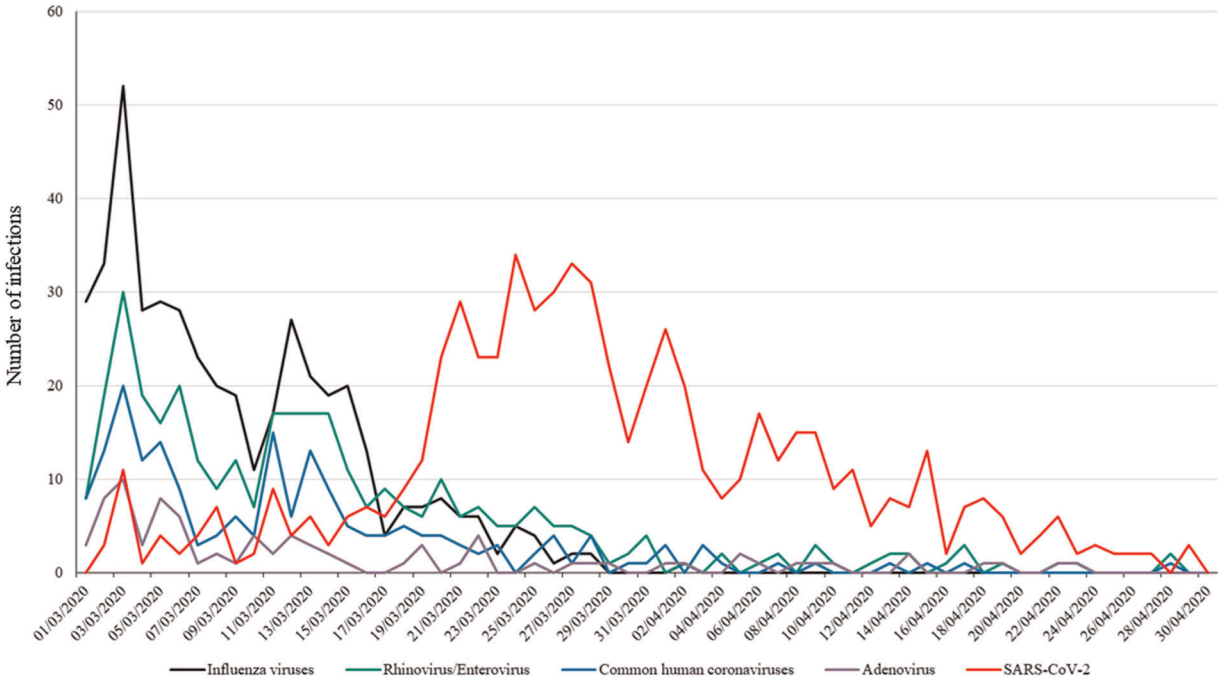

FIGURE 1 Number of infections with SARS-CoV-2 and other respiratory viruses overtime. Black line, influenza viruses; green line, rhinovirus/enterovirus; blue line, common human coronaviruses; purple line, adenovirus; red line, SARS-CoV-2

ETHICS STATEMENT

All data have been generated as part of the routine work at Assistance Publique-Hôpitaux de Marseille (Marseille university hospitals), and this study results from routine standard clinical management. The study was approved by the ethical committee of the University Hospital Institute Méditerranée Infection (No.: 2020-029). Access to the patients' biological and registry data issued from the hospital information system was approved by the data protection committee of Assistance Publique-Hôpitaux de Marseille (APHM) and was recorded in the European General Data Protection Regulation registry under number RGPD/APHM 2019-73.

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REFERENCES

1. Nowak MD, Sordillo EM, Gitman MR, Paniz Mondolfi AE. Co-infection in SARS-CoV-2 infected patients: Where are influenza virus and rhinovirus/enterovirus? *J Med Virol*. 2020;92:1699-1700. https://doi.org/10.1002/jmv.25953
2. Gaunt ER, Hardie A, Claas EC, Simmonds P, Templeton KE. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. *J Clin Microbiol*. 2010;48:2940-2947.
3. Wee LE, Ko KKK, Ho WQ, Kwek GTC, Tan TT, Wijaya L. Community-acquired viral respiratory infections amongst hospitalized inpatients during a COVID-19 outbreak in Singapore: co-infection and clinical outcomes. *J Clin Virol*. 2020;128:104436.
4. Blasco ML, Buesa J, Colomina J, et al. Co-detection of respiratory pathogens in patients hospitalized with Coronavirus viral disease-2019 pneumonia. *J Med Virol*. 2020;92:1799-1801. https://doi.org/10.1002/jmv.25922
5. Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *J Med Virol*. 2020;92:1549-1555. https://doi.org/10.1002/jmv.25781
6. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA*. 2020;323:2085-2086.

7. Amrane S, Tissot-Dupont H, Doudier B, et al. Rapid viral diagnosis and ambulatory management of suspected COVID-19 cases presenting at the infectious diseases referral hospital in Marseille, France—January 31st to March 1st, 2020: a respiratory virus snapshot. *Travel Med Infect Dis*. 2020;36: 101632.
8. Drancourt M, Michel-Lepage A, Boyer S, Raoult D. The point-of-care laboratory in clinical microbiology. *Clin Microbiol Rev*. 2016;29: 429-447.
9. Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. *Clin Microbiol Rev*. 2017; 31:e00024-17.