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Viral Co-pathogens in COVID-19 Acute Respiratory Syndrome – What Did We Learn From the First Year of Pandemic?

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Abstract

We assessed the annual occurrence and diversity of respiratory pathogens in SARS-CoV-2 positive and negative patients admitted due to acute respiratory illness (ARI). A multiplex-PCR panel targeting 23 microorganisms detected other respiratory pathogens in only 8/476 (2%) COVID-19 versus 87/463 (19%) non-COVID-19 ARI patients. Diversity and rates of pathogens vastly differed from previous years yet showed seasonal variance.

Introduction:

Acute infectious respiratory illness (ARI) is a substantial contributor to global morbidity and mortality[1]. A major decrease in the incidence of respiratory infectious diseases was noted in countries where non-pharmaceutical measures as masks, school closure and social distancing were taken to mitigate the COVID-19 pandemic[2]. Occurrence of bacterial co-pathogens or secondary infections is well described in the context of severe COVID-19 [3, 4], contributing to grave prognosis of patients with severe disease. The co-occurrence of viral and atypical pathogens in non-severe patients with COVID-19 is more diverse[5]. Likewise, the effects of the introduction of the SARS-CoV-2 to the oral microbiota are only partially studied, yet bacterial composition does not seem to be substantially altered[6]. Questions concerning carriage, transmissibility and severity of influenza and other viruses, especially during winter months, lead to speculations regarding the possible ramifications of co-infections on diagnostics, healthcare capacity and infection control measures. As the pandemic progressed in both southern and northern hemispheres, an almost universal decrease of major viral pathogens was reported[2, 7]. To assess background prevalence of respiratory pathogens and co-infections in COVID-19 patients we analyzed banked oro-nasopharyngeal specimens from patients admitted to the hospital with acute respiratory symptoms during March 1st 2020 and February 28th 2021.

Methods:

Sheba medical center (SMC) is the largest tertiary center in Israel. All oro-nasopharyngeal respiratory specimens sent for either SARS-CoV-2 testing or other workup for respiratory viruses during 2020–2021 were biobanked in -80°C. We searched the databases for patients admitted to the emergency department with acute upper and/or lower respiratory complaints (less than 14 days). Patients where considered eligible for inclusion if they had one or more of the following signs and symptoms: cough, shortness of breath, tachypnea, rhinorrhea and sore throat, not attributed to other illness. We documented presence of oxygen desaturation ($SpO_2 < 94\%$) and fever ($\geq 38°C$), and chest X-ray suggestive of lower respiratory tract infection. Excluded were patients with respiratory signs of > 14 days, patients with COVID-19 disease duration of more than 14 days, and patients hospitalized for more than 14 days during the testing time. We age-matched (+/- 5 years) acute COVID-19 patients with SARS-CoV-2 negative patients. To assess the annual prevalence of pathogens we tested 40–50 matched sample per calendric month throughout the study. Frozen oro-pharyngeal samples with sufficient residual volume were analyzed using the BioFire Filmarray® respiratory panel 2.1 (BioFire Diagnostics, UT, USA, "BioFire"). The BioFire is a sample-to-

result, multiplex, nested-PCR platform allowing rapid syndromic-based diagnoses. The respiratory panel comprises a set of 23 pathogens, mostly viral, including seasonal and non-seasonal pathogens[8]. Of note, although human rhinovirus (HRV) and enteroviruses are indiscriminate in this panel, data from the national surveillance sentinel clinics for respiratory pathogen, and data of hospitalized patients in SMC show profound activity of HRV, thus we refer to this signal as HRV. We compared characteristics of SARS-CoV-2 positive and negative patients using student's T-test. The study was conducted in accordance with the Declaration of Helsinki, informed consent was waived per Institutional Review Board (IRB) protocol, the study was approved by the SMC IRB with approval number: 7913-20-SMC

Results:

Overall, 2050 patients' electronic charts were reviewed, of which 939 (Supplementary Fig. 1 and Supplementary Table 1) were included in the analysis with valid BioFire test results. Among the 476 COVID-19 patients, 468 tested positive for SARS-CoV-2 as a single pathogen, co-pathogens were found in only 8/476 (1.6%) (Supplementary Table 2). Of the patients with ARI who were negative for SARS-CoV-2, 87/463 (18.7%) were detected with other respiratory pathogens. Pathogens detected in SARS-CoV-2 negative patients temporally varied. In March-April 2020 (spring), during the first lockdown in Israel (Fig. 1a), 25/90 (27.8%) of the non-COVID-19 patients with ARI tested positive for seasonal coronaviruses, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), influenza and parainfluenza, while human rhinovirus (HRV) was detected only in 11/90 (12.2%). In May 2020, the first lockdown was lifted, and only few patients admitted with ARI (13 tested – both groups) (Fig. 1b). During June – December 2020 we noted an almost exclusive recovery of HRV – 44/368 (11.7%), while other viruses' activity dropped to 13/368 (3.3%). During the summer and autumn months (June-November, 2020) only 11.0% (25/227) of COVID-19-negative patients with ARI were detected with respiratory pathogens. This rate nearly doubled in winter months (December 2020-February 2021), to 21.2% (30/141) with frequent HRV, yet zero cases of the usual seasonal coronaviruses, RSV and influenza that practically disappeared that winter (Fig. 1a and 1b, supplementary Table 3).

Discussion:

In this study, we report the paucity of respiratory co-pathogens detected in COVID-19 patients presenting with ARI compared with the background rates of respiratory pathogens in non-COVID-19 ARI patients. We observed seasonal changes both in incidence and variety (supplementary Table 3). While in spring 2020 we detected influenza, RSV, HMPV and seasonal coronaviruses, later in the year we saw the disappearance of those viruses with almost exclusive detection of HRV (as implied from supplementary Fig. 2). Our findings are compatible with the 2020–2021 disappearance of influenza and RSV as reported by the Israeli Center for Disease Control (ICDC)[9].

Unlike other reports addressing co-pathogen occurrence in COVID-19 patients[10–13], our study was designed to circumvent several biases: i) we included only ED admitted patients with acute respiratory complaints and age-matched them. ii) the study was annual and longitudinal with similar number of

samples per group monthly. This highly selective design overcomes biases of either secondary/nosocomial complications of severe COVID-19 patients or merely a “virome map” from testing asymptomatic COVID-19 patients.

Numerous factors presumably account for the disappearance of major respiratory viruses during COVID-19 pandemic year: social distancing, face masks, gloves and extensive hand and surface disinfection, lockdowns and flight halting. Never the less, SARS-CoV-2 incidence and prevalence were extremely high during disease surges despite these measures and the low activity of other viruses. Thus, did the new player in the "respiratory arena" displace other viral pathogens? Does these phenomena are related to intrinsic viral factors effecting epidemiological patterns of SARS-CoV-2 transmissibility compared to other respiratory viruses? A recent Australian study demonstrated that with the decline of COVID-19 and the lift of restrictions, a rise in RSV activity was detected [14]. Likewise, a reflexive rise in respiratory illness and detected viruses is noted from the ICDC latest reports[15]. However, the relatedness of the resurgence of other respiratory viruses to the actual presence of airways SARS-CoV-2 remains unanswered.

A notable observation of our study is the paucity of respiratory co-pathogens detected in COVID-19 patients. Should this observation prove consistent, it may have a significant impact on the diagnostic flow of ARI patients in high-COVID-19 prevalence zones, questioning the immediate need to search for pathogens other than SARS-CoV-2. This observation may further influence infection control policies in terms of placement of ARI patients within the emergency departments and later, hospitalization units, especially those of vulnerable patients as immunocompromised and pregnant women.

In conclusion, the annual rates of co-pathogens in Israeli COVID-19 patients with ARI were low compared with the background rates of respiratory pathogens in SARS-CoV-2 negative ARI patients. The appearance patterns of the various pathogens diverged from previous years and along the study period, with human rhinovirus being the prominent non-SARS-CoV-2 pathogen. Further studies should address the impact of SARS-CoV-2 presence *per-se* on the co-occurrence of other respiratory pathogens seasonality and diversity. Such data are of major importance for policy makers with regards to surveillance, acute illness diagnostics and infection control.

Declarations:

Transparency declaration:

All authors report no conflict of interest

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Authors' contributions:

OK: study concept and preparation, data management, analysis and interpretation, and manuscript preparation. SA, MM: study concept and design, data interpretation, and manuscript review. SGH, EL, GS, NB, and AE: manuscript review, and study supervision. RK, MO, AS, YB, OAH, RH, YA, JA, IN, LK and HS: manuscript review. All the authors have read and approved the final draft submitted.

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Figures

Figure 1a

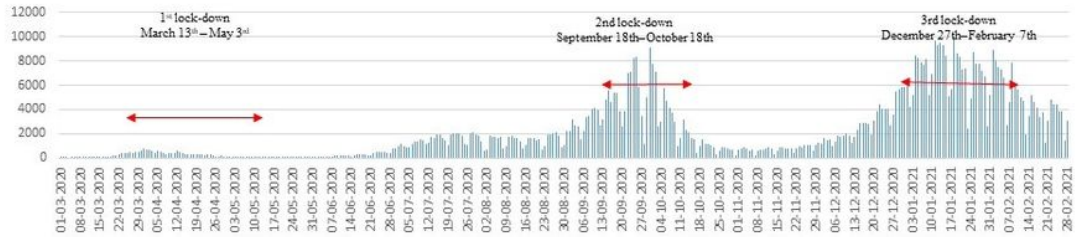

Figure 1b

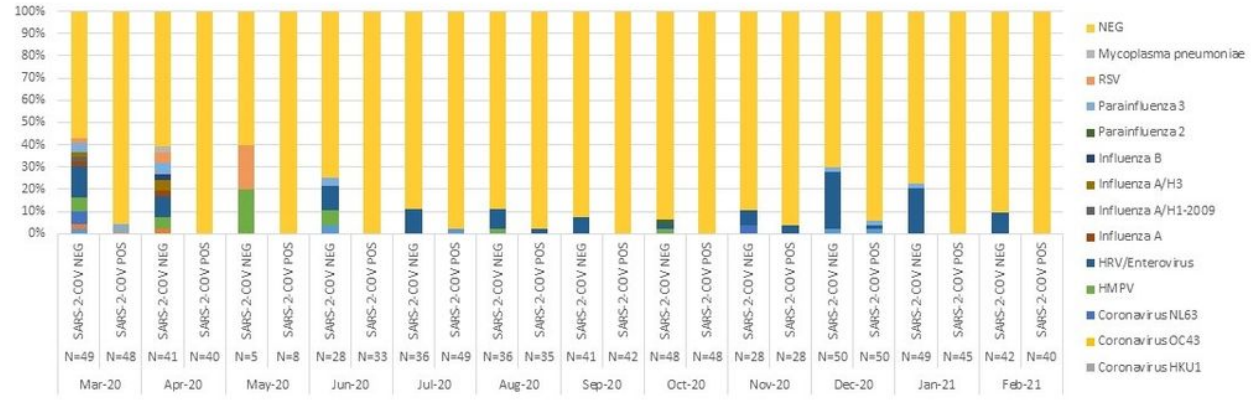

Figure 1

1a - Daily newly diagnosed COVID-19 patients, Israel MOH database 2020-2021 1b - annual pathogen distribution of patients with ARI, Israel 2020-2021

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Figures23.pptx
- SuppTable1.docx

- SuppTable2.docx
- SuppTable3.docx