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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

Objective: : This study aimed to describe the distribution of respiratory pathogens and the occurrence of co-pathogens during the first year of the COVID-19 pandemic.
Methods: We used a multiplex polymerase chain reaction (PCR) panel targeting 23 microorganisms to analyze the oro-pharyngeal samples of patients admitted to our hospital with acute respiratory infection (ARI) between March 1, 2020, and February 28, 2021. We matched 40 to 50 patients who were SARS-CoV-2 positive and SARS-CoV-2 negative per month for age and sex.
Results: A total of 939 patients with multiplex PCR test results were included in the study. Respiratory pathogens where detected in only 8/476 (1.6%) patients with COVID-19 versus 87/463 (18.7%) patients with non–COVID-19 ARI patients. Diversity and rates of pathogens vastly differed from previous years but showed seasonal variance.
Conclusion: Patients with SARS-CoV-2 infection presenting with ARI during the first year of the COVID-19 pandemic demonstrated paucity of respiratory co-pathogens.

Introduction

Acute infectious respiratory illness (ARI) is a substantial contributor to global morbidity and mortality (GBD 2016 Lower Respiratory Infections Collaborators, 2018). During the COVID-19 pandemic, a major decrease in the incidence of respiratory infectious diseases was noted in countries where non-pharmaceutical measures such as masks, school closure and social distancing were undertaken to mitigate the pandemic (Lee and Lin, 2020). Occurrence of bacterial co-pathogens or secondary infections is well described in the context of severe COVID-19 (Langford et al., 2020; Patel et al., 2021), contributing to grave prognosis of patients with severe disease. The co-occurrence of viral and atypical pathogens in COVID-19 was reported to be 11.6% (pooled prevalence) in 1 meta-analysis (Davis et al., 2020), but the studies addressing this topic are methodologically diverse. Althoughthe effects of introduction of SARS-CoV-2 to the oral microbiota are only partially studied, yet the bacterial composition does not seem to be substantially altered (Braun et al., 2021). As the pandemic progressed in both southern and northern hemispheres, an almost universal decrease of major viral pathogens was reported (Lee and Lin, 2020; Soo et al., 2020). The possible ramifications of co-infection on viral transmissibility and infectivity and the severity of co-infection are immense. Co-infections of SARS-CoV-2 and other common respiratory viral pathogens may impose additional challenges on the already stretched ambulatory and hospitalizing health care systems. Thus, valid data regarding the rate of co-infection is of utmost importance for both public health authorities and infection control units. To assess the background prevalence of respiratory pathogens and co-infections in patients with COVID-19, we analyzed the banked oro-nasopharyngeal specimens from patients admitted to the hospital with acute respiratory symptoms between March 1, 2020, and February 28, 2021.

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Methods

Setting

Sheba Medical Center (SMC) is the largest tertiary center in Israel, with 1600 hospitalization beds.

Samples collection and patients' inclusion (Supplementary Figure 1) - All oro-nasopharyngeal respiratory specimens sent for either SARS-CoV-2 testing or other workup for respiratory viruses during 2020-2021 were biobanked at −80°C. A digital list of the biobank served as the main registry for the study. For each studied month, the first eligible 40-50 consecutive cases from positive and negative cohorts were included. Patients' files were manually reviewed by an infectious disease specialist, selecting cases with ARI, either upper or lower, lasting less than 14 days. Patients were considered eligible for inclusion if they had 1 or more of the following signs and symptoms: cough, shortness of breath, tachypnea, rhinorrhea and sore throat, not attributed to other illnesses. We documented oxygen desaturation (SpO_2<94%), fever (≥38°C), and chest x-ray imaging suggestive of lower respiratory tract infection. Patients with respiratory complaints or proved COVID-19 disease duration of more than 14 days, and patients hospitalized for more than 14 days during the testing time were excluded.

Matching

Patients who received positive and negative results for SARS-CoV-2 were matched for age (±5 years) and sex to create a similar number of matched monthly cohorts (40-50 consecutive matched patients per month, accommodating for a limited number of kits).

Molecular assay

Frozen oro-nasopharyngeal samples (both SARS-CoV-2 positive and negative) with sufficient residual volume were thawed and re-analyzed using the BioFire Filmarray® respiratory panel 2.1 ("BioFire," BioFire Diagnostics, Salt Lake City, UT). 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. Of note, although human rhinovirus (HRV) and enteroviruses are not discriminable 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 referred to this signal as HRV.

Statistics

After confirming for a non-normal distribution, we used the non-parametric Mann-Whitney *U* test to compare patients' contiguous characteristics and chi-square test to compare dichotomous variables.

Ethics

The study was approved by the local institutional review board (SMC IRB approval number 7913-20-SMC).

Results

Overall, electronic charts of 2050 patients were reviewed, of which, 939 patients with valid BioFire test results (Supplementary Figure 1 and Supplementary Table 1) were included in the analysis. Among the 476 patients with COVID-19, 468 tested positive for SARS-CoV-2 as a single pathogen and 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. From March to April 2020 (spring), during the first lockdown in Israel (Figure 1a), 25/90 (27.8%) patients with ARI without COVID-19 infection tested positive for seasonal coronaviruses, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), influenza and parainfluenza viruses, whereas HRV was detected only in 11/90 (12.2%) patients. In May 2020, the first lockdown was lifted, and only few patients with ARI were admitted (13 tested – both groups) (Figure 1b). From June to December 2020, we noted an almost exclusive recovery of HRV – 44/368 (11.7%), whereas activity of other pathogens dropped to 13/368 (3.3%). During the summer and autumn months (June-November 2020), only 11.0% (25/227) of patients with ARI negative for COVID-19 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 the number of cases of the usual seasonal coronaviruses, RSV and influenza infections that practically disappeared during that winter was 0 (Figure 1a and 1b, Supplementary Table 3).

Discussion

In this study, we report the paucity of respiratory co-pathogens detected in patients with COVID-19 presenting with ARI compared with the background rates of respiratory pathogens in patients with ARI but without COVID-19. We observed seasonal changes both in incidence and variety of respiratory pathogens (Supplementary Table 3). Although in the early spring of 2020, we detected influenza, RSV, HMPV and seasonal coronaviruses, we noticed the disappearance of those viruses with almost exclusive detection of HRV later in the year (Supplementary Figure 2). Our findings are comparable with the 2020-2021 disappearance of influenza and RSV in Israel (Weinberger Opek et al., 2021).

Unlike other reports addressing co-pathogen occurrence in patients with COVID-19 (Chen et al., 2020; Kim et al., 2020, 2021; Thelen et al., 2021), our study was designed to circumvent the following biases: i) We included only patients with acute respiratory complaints admitted to the emergency department (ED) and matched them for sex and age. ii) The study was annual and longitudinal with similar number of samples analyzed per group every month. This highly selective design overcomes biases of either secondary/nosocomial complications in patients with severe COVID-19 or merely a "virome map" from testing patients with asymptomatic COVID-19.

Several factors presumably account for the disappearance of major respiratory viruses during the first year of the COVID-19 pandemic: social distancing, face masks, gloves and extensive hand and surface disinfection, lockdowns, and halting flight travel. Nevertheless, SARS-CoV-2 incidence and prevalence were extremely high during the 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? Are these phenomena related to the intrinsic viral factors affecting the epidemiological patterns of SARS-CoV-2 transmissibility compared with other respiratory viruses? Multiple studies report the resurgence of RSV worldwide throughout the second year of the pandemic (Foley et al., 2021; Weinberger Opek et al., 2021). 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 patients with COVID-19. Should this observation prove consistent, it may have a significant impact on the diagnostic flow of patients with ARI in high-COVID-19 prevalence

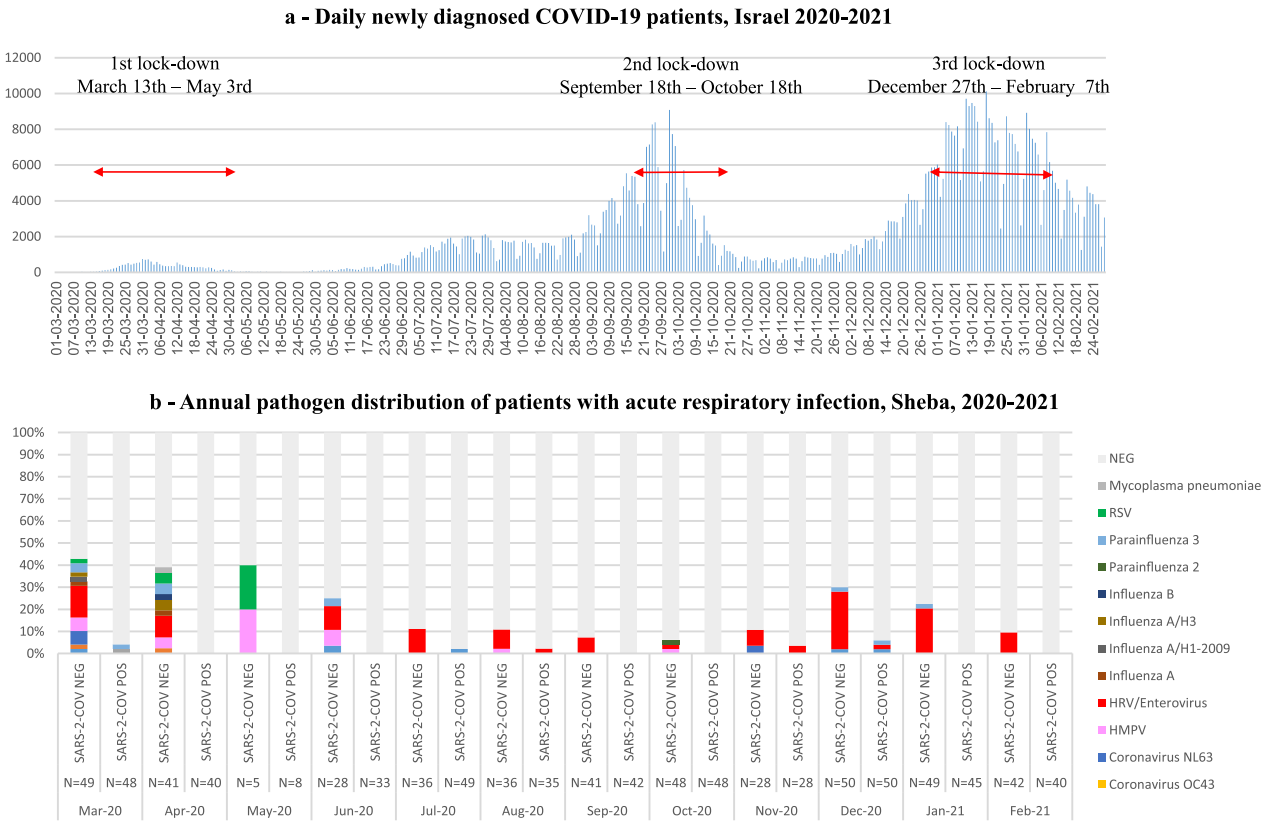

Figure 1. a - Daily newly diagnosed COVID-19 patients, Israel 2020-2021
b - Annual pathogen distribution of patients with acute respiratory infection, Sheba, 2020-2021

zones, questioning the immediate need to search for pathogens other than SARS-CoV-2. This observation may further influence the infection control policies in terms of placement of patients with ARI within the ED and, later, hospitalization units, especially those of vulnerable patients such as immunocompromised individuals and pregnant women.

This study has several limitations. Although all attempts were made to compile a calendar-balanced data set of SARS-CoV-2 positive and negative patients, in some disease nadir months, we could not reach the required 50 patients limit. In addition, the generalizability of the study is limited with regard to the younger age groups because the matching criteria could not be fulfilled because of the paucity of pediatric patients with COVID-19. Similarly, this is a single-center study, representing merely the annual local epidemiology of a unique year. Further surveillance is needed to assess the effects of SARS-CoV-2 on the personal and societal virome.

In conclusion, the annual rates of co-pathogens in Israeli patients with COVID-19 and with ARI were low compared with the background rates of respiratory pathogens in patients with ARI without SARS-CoV-2 infection. The appearance patterns of the various pathogens diverged from previous years and along the study period, with HRV 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 seasonality and diversity of other respiratory pathogens. Such data are of major importance for policy makers with regard to surveillance, acute illness diagnostics, and infection control.

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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.01.018.

References

Braun T, Halevi S, Hadar R, Efroni G, Glick Saar E, Keller N, et al. SARS-CoV-2 does not have a strong effect on the nasopharyngeal microbial composition. Sci Rep 2021;11:8922. doi:10.1038/s41598-021-88536-6.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13. doi:10.1016/S0140-6736(20)30211-7.

Davis B, Rothrock AN, Swetland S, Andris H, Davis P, Rothrock SG. Viral and atypical respiratory co-infections in COVID-19: a systematic review and meta-analysis. Journal of the American College of Emergency Physicians Open 2020. doi:10.1002/emp2.12128.

Foley DA, Yeoh DK, Minney-Smith CA, Martin AC, Mace AO, Sikazwe CT, et al. The interseasonal resurgence of Respiratory Syncytial Virus in Australian children following the reduction of Coronavirus disease 2019-related public health measures. Clin Infect Dis 2021 2020.11.11.20228692. doi:10.1093/cid/ciaa1906.

GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis 2018;18:1191–210. doi:10.1016/S1473-3099(18)30310-4.

Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. JAMA 2020;323:2085–6. doi:10.1001/jama.2020.6266.

Kim KW, Deveson IW, Pang CNI, Yeang M, Naing Z, Adikari T, et al. Respiratory viral co-infections among SARS-CoV-2 cases confirmed by virome capture sequencing. Sci Rep 2021;11:3934. doi:10.1038/s41598-021-83642-x.

Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect 2020;26:1622–9. doi:10.1016/j.cmi.2020.07.016.

Lee H-H, Lin S-H. Effects of COVID-19 Prevention Measures on Other Common Infections. Taiwan. Emerging Infect Dis 2020;26:2509–11. doi:10.3201/eid2610.203193.

Patel A, Emerick M, Cabunoc MK, Williams MH, Preas MA, Schrank G, et al. Rapid Spread and Control of Multidrug-Resistant Gram-Negative Bacteria in COVID-19 Patient Care Units. Emerging Infect Dis 2021;27:1234–7. doi:10.3201/eid2704.204036.

Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. Decreased Influenza Incidence under COVID-19 Control Measures, Singapore. Emerging Infect Dis 2020;26:1933–5. doi:10.3201/eid2608.201229.

Thelen JM, Buenen AGN, van Apeldoorn M, Wertheim HF, Hermans MHA, Wever PC. Community-acquired bacteraemia in COVID-19 in comparison to influenza A and influenza B: a retrospective cohort study. BMC Infect Dis 2021;21:199. doi:10.1186/s12879-021-05902-5.

Weinberger Opek M, Yeshayahu Y, Glatman-Freedman A, Kaufman Z, Sorek N, Brosh-Nissimov T. Delayed respiratory syncytial virus epidemic in children after relaxation of COVID-19 physical distancing measures, Ashdod, Israel, 2021. Euro Surveill 2021;26. doi:10.2807/1560-7917.ES.2021.26.29.2100706.