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Respiratory co-infections with COVID-19 in the Veterans Health Administration, 2020

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ABSTRACT

Reporting of Coronavirus disease 2019 (COVID-19) co-infections with other respiratory pathogens has varied. We evaluated 825,280 molecular and/or viral culture respiratory assays within the Veterans Health Administration from September 29, 2019 to May 31, 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in 10,222 of 174,746 (5.8%) individuals. 30,063 (17.2%) of 174,746 individuals tested for SARS-CoV-2 had additional respiratory pathogen testing; co-infection was identified in 56 of 3757 (1.5%) individuals positive for SARS-CoV-2. Among those negative for SARS-CoV-2, 1022 of 26,306 (3.9%) were positive for at least 1 respiratory pathogen. Compared to COVID-19 mono-infection, individuals with COVID-19 co-infection had lower odds of being female. Compared to non-COVID-19 respiratory pathogen infection, individuals with COVID-19 co-infection had lower odds of being female, were hospitalized more frequently, had higher odds of death, and were younger at death. Our findings suggest COVID-19 co-infections were rare; however, not all COVID-19 patients were concurrently tested for other respiratory pathogens and seasonal decreases in other respiratory pathogens were occurring as COVID-19 emerged.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan, China and is an ongoing pandemic. The first U.S. cases occurred in January 2020 and as of December 22, 2020 there were 17,790,376 reported cases and 316,844 deaths in the United States (Centers for Disease Control and Prevention. Coronavirus Disease 2020c). Much is still being learned about this virus as well as the potential for patients to have concurrent respiratory illnesses. Based on initial reports from China, co-infection with COVID-19 and other respiratory pathogens was thought to be uncommon (Chen et al., 2020). Early in the pandemic, U.S. testing resources were limited and in some settings specimens were reflexed to SARS-CoV-2 testing only after an initial influenza and/or respiratory panel test were negative. In the U.S., if an alternative respiratory pathogen diagnosis was made, SARS-CoV-2 testing was not performed which may have hindered the identification of COVID-19 positive patients as well as COVID-19 co-infected patients early in the pandemic (Centers for Disease Control and Prevention, 2020d, Khaddour et al., 2020).

The prevalence and outcomes for COVID-19 patients with respiratory co-infections is not well described. Small case studies and series have documented the presence of COVID-19 co-infections including influenza in adults (Azekawa et al., 2020; Blasco et al., 2020; Boschi et al., 2020; Cuadrado-Payan et al., 2020; Ding et al., 2020; Fan et al., 2020; Khodamoradi et al., 2020; Konala et al., 2020; Lin et al., 2020; Ma et al., 2020; Motta and Gomez, 2020; Nowak et al., 2020; Ozaras et al., 2020; Touzard-Romo et al., 2013; Wee et al., 2020; Wu et al., 2020; Xie et al., 2020; Zhu et al., 2020). Zhu et al. described 24 pathogens that were identified when COVID-19 specimens were tested for 39 respiratory pathogens (Zhu et al., 2020). The reported prevalence of COVID-19 co-infections varies greatly. Zhu et al reported 94.2% of 257 patients with COVID-19, had viral, bacterial and fungal co-infections with viruses being found in 31.5% of cases some of which were noted to possibly be co-colonization (Zhu et al., 2020). Other reports noted a COVID-19 co-infection prevalence of 0.54% to 20.7% (Hazra et al., 2020, Kim et al., 2020, Ozaras et al., 2020, Richardson et al., 2020). These authors did not all report on patients' demographics, co-morbidities, treatments and outcomes.

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We investigated the prevalence, demographics and outcomes of patients with COVID-19 co-infections with other respiratory pathogens compared to patients with COVID-19 mono-infection (where other respiratory pathogen testing was negative) as well as patients with non-COVID-19 respiratory pathogens (where SARS-CoV-2 testing negative) in Veterans Health Administration (VHA) during the early pandemic period from February to May 2020.

2. Methods

Molecular and viral culture laboratory test results were identified from the VHA Corporate Data Warehouse for individuals tested in any of the 1225 inpatient or outpatient VHA health care facilities from all 50 states as well as the District of Columbia and Puerto Rico from September 29, 2019 (the start of the 2019–2020 influenza season) through May 31, 2020 for respiratory pathogens (adenovirus, *Bordetella pertussis, Bordetella parapertussis, Chlamydia pneumoniae*, SARS-CoV-2, other coronaviruses [HKU1, NL63, 229E, and OC43], influenza A and B, human metapneumovirus [hMPV], human parainfluenza viruses [HPIV], *Mycoplasma pneumoniae*, rhinovirus and/or enterovirus, and respiratory syncytial virus [RSV]). U.S. FDA approved multiplex respiratory pathogen panels varied across VHA facilities and commercial labs. Supplementary Table S1 shows respiratory pathogen panels that were available through commercial labs. Bacterial and fungal cultures and antibody test results for SARS-CoV-2 and other respiratory pathogens were excluded. Molecular and viral culture laboratory tests for respiratory pathogens were limited to February 1, 2020 through May 31, 2020, after the COVID-19 pandemic had begun. Individuals who had a U.S. FDA Emergency Use Authorization approved SARS-CoV-2 molecular test and were also tested for other respiratory pathogens within 7 days of a SARS-CoV-2 test collection date were included. Three groups were identified: (1) COVID-19 co-infected individuals defined as those who tested positive for SARS-CoV-2 plus at least one other respiratory pathogen through molecular testing or viral culture; (2) COVID-19 mono-infected individuals defined as those who tested positive for SARS-CoV-2 and tested negative for other respiratory pathogens; and (3) Non-COVID-19 respiratory pathogen infected individuals defined as those who tested positive for at least 1 respiratory pathogen but tested negative for SARS-CoV-2. Available demographic data, hospitalizations, and outcomes were obtained for individuals in all groups. State where the individual was tested was evaluated based on U.S. Census regions (U.S. Department of Commerce – Economics and Statistics Administration. U.S. Census Bureau 2021). Differences in proportions were analyzed using the χ^2 or Fisher's exact tests (Open Epi version 3.01, Atlanta, GA), odds ratios (OR) and confidence intervals (CI) were calculated, and P value < 0.05 was considered statistically significant (Dean et al., 2013).

Access to data for public health activities is covered under the Privacy Act of 1974; System of Records entitled "National Patient Databases-VA" (121VA10P2) as set forth in the Federal Register 79 FR 8245 (Department of Veterans Affairs Office of Research & Development, 2019). The data utilized in this study were obtained for the purpose of public health operations in VHA. No additional analyses were performed outside of public health operational activities; thus, it did not require VHA or facility Institutional Review Board review in accordance with 2019 Department of Veterans Affairs Office of Research & Development Program Guide 1200.21, VHA Operations Activities that May Constitute Research.

3. Results

A total of 825,280 respiratory pathogen tests (including SARS-CoV-2) were performed between September 2019 and May 2020. Of these, 617,539 tests were performed starting in February 2020, after the COVID-19 pandemic had begun (Table 1). There was a decrease in percent positivity of influenza, rhinovirus and/or enterovirus and hMPV between surveillance weeks 8 to 11, 2020, while SARS-CoV-2 test percent positivity started rising in week 10 (Fig. 1).

Table 1
Respiratory pathogen identification in Veterans Health Administration, February 1, 2020 to May 31, 2020.

Pathogen	Total positive	# Tests	Unique positives	Unique total
Nonspecific only[a]	393	2874	385	2669
Viral culture only[a]	0	80	0	79
Adenovirus	117	20,879	115	19,286
Bordetella pertussis	59	17,051	59	15,817
Bordetella parapertussis	2	5681	2	5281
Chlamydia pneumoniae	63	18,057	63	16,698
Coronaviruses (HKU1, NL63, 229E, & OC43)	582	65,744	554	16,373
SARS-CoV-2[b]	14,838	227,109	10,222	174,746
Influenza A/B	12,121	83,648	12,112	80,942
Human metapneumovirus	544	19,397	538	17,932
Human parainfluenza viruses (I-IV)	182	74,127	177	18,024
Mycoplasma pneumoniae	71	18,199	68	16,806
Rhinovirus-enterovirus	1144	19,420	1117	17,994
Respiratory syncytial virus	903	45,273	865	38,291
Total	31,019	617,539	26,277	440,938

[a] Nonspecific Only and Viral Culture Only were tests that did not specify which respiratory pathogens were tested.
[b] SARS-CoV-2 test positivity/unique patients due to serial testing among some patients.

Of 227,109 SARS-CoV-2 tests performed (174,746 individuals), there were 14,838 (6.5%) positive tests (10,222 individuals). A total of 30,063 of 174,746 (17.2%) individuals with SARS-CoV-2 testing had at least one other respiratory pathogen test performed within 7 days of their SARS-CoV-2 test; of these, 3,757 (12.5%) individuals were positive for SARS-CoV-2. Of the 3,757 individuals who tested positive for SARS-CoV-2 and were tested for at least one other respiratory pathogen, COVID-19 co-infection was found in 56 (1.5%) individuals, while 3,701 (98.5%) were COVID-19 mono-infected. Among 26,306 individuals negative for SARS-CoV-2 and tested for other respiratory pathogens, 1,022 (3.9%) were positive for at least 1 non-COVID-19 respiratory pathogen.

Of the 56 individuals with COVID-19 co-infection, there were 19 rhinovirus and/or enterovirus, 15 influenza (12 influenza A and 3 influenza B), 13 with a non-COVID-19 coronavirus, 4 RSV, 3 hMPV, 2 HPIV, 2 adenovirus, and 1 *C. pneumoniae* (Table 2). Three individuals were identified with more than 1 other respiratory pathogen (2 with coronavirus NL63 and adenovirus and 1 with a coronavirus NL63 and rhinovirus/enterovirus). No COVID-19 co-infections with *B. pertussis and/or B. parapertussis* or *M. pneumoniae* were identified. Table 2 summarizes characteristics of COVID-19 co-infected, COVID-19 mono-infected, and non-COVID-19 respiratory pathogen infected individuals and Table 3 compares characteristics of COVID-19 co-infected individuals to COVID-19 mono-infected and non-COVID-19 respiratory pathogen infected individuals.

3.1. Demographic characteristics

The COVID-19 co-infected group had fewer females compared to both the COVID-19 mono-infected and the non-COVID-19 respiratory pathogen infected group ($P = 0.03$, OR 0.2, 95% CI 0.008–0.8; $P = 0.01$,

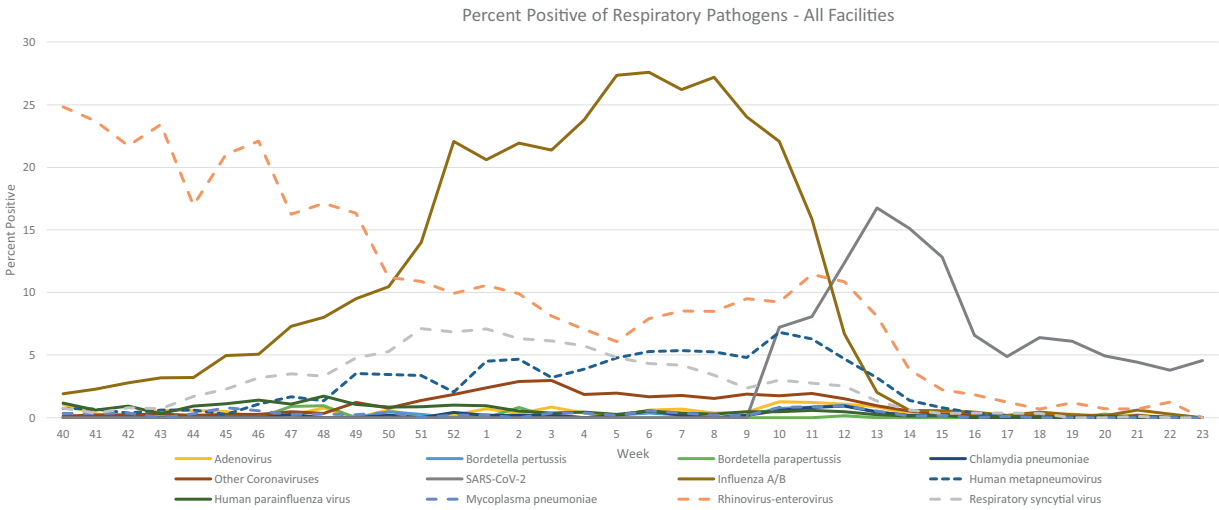

Fig. 1. Percent positivity of respiratory pathogens in Veterans Health Administration, September 29, 2019 to May 31, 2020.

Table 2
Characteristics of COVID-19 co-infected, COVID-19 mono-infected, and non-COVID-19 respiratory infected individuals, Veterans Health Administration, 2/1/2020-5/31/2020.

Characteristics	COVID-19 co-infected[a] *N* = 56	COVID-19 mono-infected[b] *N* = 3701	Non-COVID-19 respiratory pathogen infected[c] *N* = 1022
Gender, no. (%)			
• Female	1 (2)	391 (11)	147 (14)
• Male	55 (98)	3310 (89)	875 (86)
Median age (IQR)	68 (56–74)	63 (51–72)	61 (46–71)
Age groups			
• <45 years old	9 (16)	591 (16)	242 (24)
• 45–64 years old	14 (25)	1376 (37)	351 (34)
• 65–84 years old	28 (50)	1490 (40)	368 (36)
• 85+ years old	5 (9)	244 (7)	61 (6)
Deaths, no. (%)	10 (18)	502 (14)	73 (7)
Median age (IQR)	64.5 (61–71)	74 (69–85)	78 (70–87)
Age groups			
• <45 years old	0 (0)	2 (<1)	0 (0)
• 45–64 years old	5 (50)	79 (16)	6 (8)
• 65–84 years old	4 (40)	293 (58)	41 (56)
• 85+ years old	1 (10)	128 (25)	26 (36)
Hospitalization,[e] no (%)	38 (68)	2133 (58)	440 (43)
Remained hospitalized as of 30 June, 2020	3 (8)	211 (10)	21 (5)
Median length of stay, days (IQR)	7 (4–16)	9 (4–15)	4 (2–7)
Length of stay, days (%)			
• <3 days	4 (12)	323 (17)	134 (32)
• 3–7 days	15 (43)	629 (33)	191 (45)
• 8–14 days	5 (14)	469 (24)	40 (10)
• 15–30 days	6 (17)	268 (14)	28 (7)
• >30 days	5 (14)	233 (12)	26 (6)
ICU, no (%)	10 (26)	796 (37)	107 (24)
Median ICU length of stay, days (IQR)	6 (4–16)	8 (4–15)	4 (2–7)
Length of ICU stay, days (%)			
• <3 days	2 (20)	120 (15)	35 (33)
• 3–7 days	3 (30)	256 (32)	46 (43)
• 8–14 days	2 (20)	197 (25)	14 (13)
• 15–30 days	3 (30)	158 (20)	8 (7)
• >30 days	0 (0)	65 (8)	4 (4)
Rural-urban,[f] no. (%)			
• Highly rural	0 (0)	5 (<1)	5 (<1)
• Rural	8 (14)	316 (8)	181 (18)
• Urban	48 (86)	3375 (91)	832 (81)
• Unknown	0 (0)	5 (<1)	4 (<1)
Median body mass index (BMI) (IQR)	28.2 (24.3–34.2)	29.5 (25.7–34)	29.3 (24.9–33.6)
Underweight (BMI <18.5)	3 (5)	65 (2)	19 (2)
Normal (BMI 18.5-24.9)	13 (23)	688 (19)	235 (23)
Overweight (BMI 25-29.9)	17 (31)	1108 (30)	276 (27)
Obese (BMI ≥30)	22 (39)	1694 (45)	459 (45)
Unknown, no. (%)	1 (2)	146 (4)	33 (3)

(*continued*)

Table 2 (*Continued*)

Characteristics	COVID-19 co-infected[a] *N* = 56	COVID-19 mono-infected[b] *N* = 3701	Non-COVID-19 respiratory pathogen infected[c] *N* = 1022
Race, no. (%)			
Black or African American	20 (36)	1859 (50)	214 (21)
White	27 (48)	1384 (37)	675 (66)
Multiracial	0 (0)	37 (1)	8 (<1)
Other race identified[g]	1 (2)	92 (3)	40 (4)
Unknown/missing	8 (14)	329 (9)	85 (8)
Ethnicity, no. (%)			
Hispanic or Latino	6 (11)	388 (10)	75 (7)
Not Hispanic or Latino	44 (78)	3067 (83)	873 (86)
Unknown/missing	6 (11)	246 (7)	74 (7)
Respiratory pathogens identified[h]	*N* = 59		*N* = 1062
Adenovirus	2 (3)	NA	28 (3)
Bordetella pertussis/parapertussis	0 (0)	NA	0 (0)
Chlamydia pneumoniae	1 (2)	NA	5 (<1)
Coronaviruses (HKU1, NL63, 229E, & OC43)	13 (22)	NA	122 (11)
Human metapneumovirus (hMPV)	3 (5)	NA	145 (14)
Human parainfluenza virus (HPIV I-IV)	2 (3)	NA	31 (3)
Influenza	15 (26)	NA	245 (23)
Influenza A	12 (80)	NA	187 (77)
Influenza B	3 (20)	NA	54 (22)
Influenza unspecified	0 (0)	NA	3 (1)
Mycoplasma pneumoniae	0 (0)	NA	6 (<1)
Respiratory syncytial virus (RSV)	4 (7)	NA	101 (10)
Rhinovirus/enterovirus	19 (32)	NA	379 (35)
Multiple pathogens identified[i]:	*N* = 2	*N* = NA	*N* = 28
Adenovirus + influenza A	0	NA	2
Adenovirus + hMPV + rhinovirus[d]	0	NA	1
Adenovirus + non-COVID-19 coronavirus	1	NA	0
Adenovirus + rhinovirus[d]	0	NA	5
hMPV + influenza A	0	NA	1
hMPV + influenza A + rhinovirus[d]	0	NA	1
hMPV + non-COVID-19 coronavirus	0	NA	1
hMPV + non-COVID-19 coronavirus + rhinovirus[d]	0	NA	1
hMPV + rhinovirus[d]	0	NA	1
HPIV I-IV + RSV	0	NA	1
HPIV I-IV + rhinovirus[d]	0	NA	2
Influenza A + non-COVID-19 coronavirus	0	NA	1
Influenza A + rhinovirus[d]	0	NA	3
Influenza B + non-COVID-19 coronavirus	0	NA	1
Non-COVID-19 coronavirus + RSV	1	NA	1
Non-COVID-19 coronavirus + rhinovirus[d]	1	NA	4
RSV + rhinovirus[d]	0	NA	2

IQR = interquartile range.

[a] COVID-19 co-infected individuals were defined as those who tested positive for SARS-CoV-2 and at least one other respiratory pathogen through molecular testing or viral culture.

[b] COVID-19 mono-infected individuals were defined as those who tested positive for SARS-CoV-2 and were negative for other respiratory pathogens.

[c] Non-COVID-19 respiratory pathogen infected individuals were those who tested positive for at least 1 respiratory pathogen but tested negative for SARS-CoV-2.

[d] Rhinovirus = rhinovirus/enterovirus.

[e] Hospitalized patients include nursing home, long term care and rehabilitation patients.

[f] Rural-Urban definitions (U.S. Department of Veterans Affairs 2020): Urban Area: Census tracts with at least 30 percent of the population residing in an urbanized area as defined by the Census Bureau. Rural Area: Land areas not defined as urban or highly rural. Highly rural area: sparsely populated areas – less than 10 percent of the working population commutes to any community larger than an urbanized cluster, which is typically a town of no more than 2500 people.

[g] Other races identified - American Indian or Alaska Native, Asian, Native Hawaiian, or Other Pacific Islander.

[h] Total *N* reflects that some patients had more than 1 pathogen identified.

[i] Infection within 14 days of each other.

OR 0.1, 95% CI 0.005–0.6). The median (interquartile range) age was 68 years (56–74) for COVID-19 co-infected, 63 years (51–72) for COVID-19 mono-infected, and 61 years (46–71) for non-COVID-19 respiratory pathogen infected. There was no statistical difference between individual age groups. The highest proportion of individuals in all 3 groups were from urban areas but this was not statistically significant. The predominant races were Black and/or African American and White with >70% not of Hispanic or Latino ethnicity. Compared to White individuals, Black and/or African American individuals had higher odds of COVID-19 co-infection versus the non-COVID-19 respiratory pathogen infected group (P = 0.007, OR 2.3, 95% CI 1.3–4.3). Although not statistically different between the 3 groups, the median body mass index was in the overweight category for all groups (28.2–29.5). All 3 groups had individuals from states across the 4 U.S. Census regions.

3.2. Outcomes

There were significantly more hospital admissions in the COVID-19 co-infected group compared to the non-COVID-19 respiratory pathogen infected group ($P \leq 0.001$, OR 2.8, 95% CI 1.6–5.1), but hospitalizations did not differ compared to COVID-19 mono-infected (P = 0.2, OR 1.6, 95% CI 0.9–2.8). The median (interquartile range) length of hospitalization in days was 7 (4–16); for COVID-19 co-infected, 9 (4–15) for COVID-19 mono-infected, and 4 (2–7) for non-COVID-19 respiratory pathogen infected. There were no statistical differences among subgroups of varying length of hospitalization. Intensive care unit admissions also did not differ between the 3 groups. Odds of death were significantly higher with 10 of 56 (18%) COVID-19 co-infected compared to 73 of 1022 (7%) of non-COVID-19 respiratory pathogen infected individuals

Table 3
Comparisons between COVID-19 co-infected, COVID-19 mono-infected, and non-COVID-19 respiratory infected individuals.

Characteristics	COVID-19 co-infected[a] vs COVID-19 mono-infected[b] Odds Ratios (95% CI)	COVID-19 co-infected[a] vs COVID-19 mono-infected[b] *P* value[d]	COVID-19 co-infected[a] vs non-COVID-19 respiratory pathogen infected[c] Odds Ratio (95% CI)	COVID-19 co-infected[a] vs non-COVID-19 respiratory pathogen infected[c] *P* value[d]
Gender				
• Female	0.2 (0.008–0.8)	**0.03**	0.1 (0.005–0.6)	0.01
• Male		referent		referent
Age groups				
• <45 years old	0.8 (0.4–1.7)	0.7	0.5 (0.2–1)	0.9
• 45–64 years old	0.5 (0.3–1)	0.08	0.5 (0.3–1)	0.07
• 65–84 years old		referent		referent
• 85+ years old	1.1 (0.4–2.7)	>1[e]	1.1 (0.4–2.8)	>1[e]
• Deaths	1.4 (0.7–2.7)	0.5	2.8 (1.3–5.7)	**0.02**[e]
• *Age groups*				
• <45 years old	0 (0–285.1)	>1[e]	NA	NA
• 45–64 years old	4.6 (1.1–19.7)	0.06[e]	8.1 (1.6–43.4)	**0.02**[e]
• 65–84 years old		referent		referent
• 85+ years old	0.6 (0.02–4.6)	>1[e]	0.4 (0.02–3.4)	0.7[e]
Hospitalization[f]	1.6 (0.9–2.8)	0.2	2.8 (1.6–5.1)	**0.0005**
Length of stay, days				
• <3 days	0.5 (0.1–1.5)	0.4	0.4 (0.1–1.1)	0.1
• 3–7 days		referent		referent
• 8–14 days	0.4 (0.1–1.2)	0.2	1.6 (0.5–4.5)	0.6[e]
• 15–30 days	0.9 (0.3–2.4)	0.9	2.7 (0.9–7.5)	0.1[e]
• >30 days	0.9 (0.3–2.4)	1	2.4 (0.7–7.1)	0.2
ICU				
Length of ICU stay, days	0.6 (0.3–1.2)	0.2	1.1 (0.5–2.3)	1
• <3 days	1.4 (0.2–9.7)	>1[e]	0.9 (0.1–6.2)	>1[e]
• 3–7 days		referent		referent
• 8–14 days	0.9 (0.1–5.9)	>1[e]	2.2 (0.2–15.9)	0.7[e]
• 15–30 days	1.6 (0.3–9.5)	0.8[e]	5.5 (0.8–37.4)	0.1[e]
• >30 days	0 (0–6.9)	>1[e]	0 (0–24.5)	>1[e]
Rural-Urban[g]				
• Highly rural	0 (0–58.8)	>1[e]	0 (0–14.5)	>1[e]
• Rural	1.8 (0.8–3.7)	0.2[e]	0.8 (0.3–1.6)	0.6
• Urban		referent		referent
• Unknown	0 (0–58.8)	>1[e]	0 (0–19.7)	>1[e]
Body mass index (BMI)				
• Underweight (BMI <18.5)	2.4 (0.5–8.2)	0.3[e]	2.8 (0.6–10.3)	0.3[e]
• Normal (BMI 18.5–24.9)		referent		referent
• Overweight (BMI 25–29.9)	0.8 (0.4–1.7)	0.7	1.1 (0.5–2.4)	0.9
• Obese (BMI ≥30)	0.7 (0.3–1.4)	0.4	0.9 (0.4–1.8)	0.8
• Unknown, no. (%)	0.4 (0.02–2.1)	0.5[e]	0.5 (0.02–3.3)	1[e]
Race				
• Black or African American	0.6 (0.3–1)	0.06	2.3 (1.3–4.3)	**0.007**
• White		referent		referent
• Multiracial	0 (0–4.6)	1[e]	0 (0–11.9)	>1[e]
• Other race identified[h]	0.6 (0.03–3)	0.9[e]	0.6 (0.03–3.5)	>1[e]
• Unknown/missing	1.2 (0.5–2.7)	0.7	2.4 (1–5.2)	0.08[e]
Ethnicity				
• Hispanic or Latino	1.1 (0.4–2.4)	1	1.6 (0.6–3.7)	0.4[e]
• Not Hispanic or Latino		referent		referent
• Unknown/missing	1.7 (0.7–3.8)	0.3[e]	1.6 (0.6–3.7)	0.4[e]

[a] COVID-19 co-infected individuals were defined as those who tested positive for SARS-CoV-2 and at least one other respiratory pathogen through molecular testing or viral culture.
[b] COVID-19 mono-infected individuals were defined as those who tested positive for SARS-CoV-2 and were negative for other respiratory pathogens.
[c] Non-COVID-19 respiratory pathogen infected individuals were those who tested positive for at least 1 respiratory pathogen but tested negative for SARS-CoV-2.
[d] *P* values were determined by χ^2 test, unless specified otherwise. Significant values are in bold.
[e] *P* values were determined by Fisher's exact test.
[f] Hospitalized patients include nursing home, long term care and rehabilitation patients.
[g] Rural-Urban definitions (U.S. Department of Veterans Affairs 2020): Urban Area: Census tracts with at least 30 percent of the population residing in an urbanized area as defined by the Census Bureau. Rural Area: Land areas not defined as urban or highly rural. Highly Rural Area: Sparsely populated areas – less than 10 percent of the working population commutes to any community larger than an urbanized cluster, which is typically a town of no more than 2500 people.
[h] Other races identified - American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander.

(*P* = 0.02, OR 2.8, 95% CI 1.3–5.7), however there was no statistical difference compared to COVID-19 mono-infected (502 of 3701 [14%], *P* = 0.5, OR 1.4, 95% CI 0.7–2.7). The 45 to 64 year-old age group was statistically more likely to die compared to 65 to 84 year-old age group in the COVID-19 co-infected versus the non-COVID-19 respiratory pathogen infected group (*P* = 0.02, OR 8.1, 95% CI 1.6–43.4). Of those who had COVID-19 co-infection and died, 4 had rhinovirus and/or enterovirus, 2 had a non-COVID-19 coronavirus, 1 influenza, 1 hMPV, 1 HPIV, and 1 RSV.

4. Discussion

Initial U.S. testing algorithms for COVID-19 recommended having a negative influenza test and/or respiratory viral panel prior to performing COVID-19 testing, however this guidance was subsequently modified (Centers for Disease Control and Prevention, 2020d, Khaddour et al., 2020). During the 2020 to 2021 respiratory virus season, clinicians need to have heightened awareness that co-infections with COVID-19 can and do exist and the presence of other respiratory

pathogens should not preclude testing for COVID-19 and vice versa. During the early phase of the pandemic in VHA, COVID-19 co-infections with other respiratory pathogens were rare and lower than previously reported (Hazra et al., 2020; Kim et al., 2020; Ozaras et al., 2020; Richardson et al., 2020; Zhu et al., 2020). However, there was a decrease in other respiratory pathogens detected starting in weeks 8 to 11 which may have been related to ongoing public health messages such as mask wearing and social distancing.

While there are many published case reports and series of COVID-19 co-infection, there are relatively few studies that compare COVID-19 co-infected, COVID-19 mono-infected, and non-COVID-19 respiratory pathogen infected individuals. In our study, one of the larger comparisons of COVID-19 co-infected individuals, COVID-19 co-infected individuals were similar to COVID-19 mono-infected individuals but different from non-COVID-19 respiratory pathogen infected individuals. We found that when compared with COVID-19 mono-infected, COVID-19 co-infected patients were less likely to be female and there were no differences between age groups. In comparison, Hazra et al noted those with COVID-19 co-infection were younger while Kim et al noted no age difference between COVID-19 co-infected and COVID-19 mono-infected patients (Hazra et al., 2020; Kim et al., 2020). Similar to other studies, rhinovirus and/or enterovirus was the most common respiratory pathogen we identified in COVID-19 co-infected patients (Hazra et al., 2020; Kim et al., 2020; Richardson et al., 2020). Less has been reported on COVID-19 co-infections compared to non-COVID-19 respiratory pathogen infected individuals during the pandemic. In our study, when COVID-19 co-infected were compared to non-COVID-19 respiratory pathogen infected, those individuals were less likely to be female, but were more likely to be Black and/or African American, had more hospitalizations, had a higher odd of death, and were younger at the time of death. Xie et al also noted that COVID-19 infected patients (without COVID-19 co-infection) were more likely to have extrapulmonary organ dysfunction, death, admission to an Intensive care unit and longer hospital length of stay compared to seasonal influenza infected patients (Xie et al., 2020). Further analysis of factors contributing to these findings are warranted.

Our study has limitations. Detection of COVID-19 co-infections in our cohort may have been limited since only 17.2% of patients with SARS-CoV-2 testing were also tested for other respiratory pathogens during the study period making the 1.5% found with COVID-19 co-infection likely an underestimation of COVID-19 co-infections. We also did not analyze bacterial or fungal co-infections that were not part of a standard respiratory panel, whether identified infections were health care-associated or what treatments patients received. As the onset of the COVID-19 pandemic began at the tail end of 2019-20 influenza season, other respiratory pathogen positivity was decreasing and therefore identification of other non-COVID respiratory pathogens was likely lower than it would have been earlier in the winter. In addition, SARS-CoV-2 testing was both policy dependent and at the discretion of the provider. Testing was also initially reserved for those with symptoms who presented to VHA health care facilities, which could have limited detection of asymptomatic or more mild cases of COVID-19 (or other non-COVID respiratory pathogens) that didn't seek medical attention or avoided in-person visits to VA medical centers for evaluation. There was also widespread reagent and consumable shortages, which could have affected SARS-CoV-2 and respiratory pathogen testing availability. The number of tests performed varied across respiratory pathogens as there was no standardized test for respiratory pathogens in use across all VHA facilities. Some facilities performed testing in-house while others sent specimens to commercial laboratories with multiple respiratory pathogen panels available (Supplementary Table S1). Additionally, COVID-19 or other respiratory pathogen testing results performed at outside, non-VHA health care settings may not have been available within the VHA electronic health record.

COVID-19 co-infections in VHA were detected with 8 different viral and bacterial respiratory pathogens, with over 60% of co-infected individuals hospitalized. Providers should be reminded that testing for other respiratory pathogens in patients with COVID-19 should be considered, particularly those with more severe illnesses and when other pathogens are known to be circulating as per U.S. Centers for Disease Control and Prevention guidance (Centers for Disease Control and Prevention 2020a; Centers for Disease Control and Prevention 2020b). Identification of COVID-19 co-infections with respiratory pathogens with possible treatments (*B. pertussis, B. parapertussis, C. pneumoniae, M. pneumoniae*, and influenza) are particularly important. Diagnostic tests are now incorporating SARS-CoV-2 in multiplex panels, which should result in improved understanding and identification of co-infections. Influenza vaccination and prevention efforts during influenza season will be particularly important as COVID-19 co-infection with influenza was the second most common co-infection that we identified in VHA. Further comparisons of COVID-19 co-infected versus COVID-19 mono-infected and non-COVID-19 respiratory infected individuals to assess any differences in clinical presentation, co-morbid conditions, severity, outcomes, complications and actionable results will be important as the pandemic evolves and COVID-19 vaccines become widely available.

Author Statement

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Declaration of Competing Interest

The authors declare that they have no competing interests. The views expressed in this paper are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Author Contributions

Schirmer: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Writing – Original Draft, Visualization; Lucero-Obusan: Conceptualization, Methodology, Validation, Writing – Review & editing; Sharma: Methodology, Formal analysis, Writing – Review & editing; Sohoni: Software, Data curation; Oda: Conceptualization, Methodology, Writing – Review & editing, Supervision; Holodniy: Conceptualization, Methodology, Writing – Review & editing, Supervision

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.diagmicrobio.2021.115312.

References

Azekawa S, Namkoong H, Mitamura K, Kawaoka Y, Saito F. Co-infection with SARS-CoV-2 and influenza A virus. IDCases 2020;20:e00775. doi: 10.1016/j.idcr.2020.e00775.

Blasco ML, Buesa J, Colomina J, Forner MJ, Galindo MJ, Navarro J, et al. Co-detection of respiratory pathogens in patients hospitalized with Coronavirus viral disease-2019 pneumonia. J Med Virol. 2020;92:1799–1801.

Boschi C, Hoang V, Giraud-Gatineau A, Ninove L, Lagier J, La Scola B, et al. Co-infections with SARS-CoV-2 and other respiratory viruses in Southeastern France: a matter of sampling time. J Med Virol. 2020. https://doi.org/10.1002/jmv26692.

Centers for Disease Control and Prevention. Information for clinicans on influenza viral testing. November 2020a. [9th December 2020]. Available https://www.cdc.gov/flu/professionals/diagnosis/index.htm.

Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). December 2020b. [9th December 2020]. Available https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.

Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) Cases in the U.S. 2020c. [22nd December 2020]. Available https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html.

Centers for Disease Control and Prevention. Overview of Testing for SARS-CoV-2. 2020d. [20th March 2020]. Available https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html. Published 14 March 2020.

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(10223):507–13.

Cuadrado-Payan E, Montagud-Marraha E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet 2020;395(10236):e84. doi: 10.1016/S0140-6736(20)31052-7 Epub 2020 May 5.

Dean AG, Sullivan KM, Soe MM. OpenEpi - Open Source Epidemiologic Statistics for Public Health, 2013 Version. [24th November 2020]. Available http://www.openepi.com/Menu/OE_Menu.htm. Updated 6 April 2013.

Department of Veterans Affairs Office of Research & Development. Program Guide 1200.21, VHA operations activities that may constitute research. 2019. [9th December 2020]. Available https://www.research.va.gov/resources/policies/ProgramGuide-1200-21-VHA-Operations-Activities.pdf.

Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients co-infected with 2019 noval coronavirus and influenza virus in Wuhan, China. J Med Virol. 2020. https://doi.org/10.1002/jmv.25871.

Fan B, Lim K, Chong V, Chan S, Ong K, Kuperan P. COVID-19 and mycoplasma pneumoniae coinfection. Am J Hematol 2020;95(6):723–4. doi: 10.1002/ajh.25785 Epub 2020 Apr 3.

Hazra A, Collison M, Pisano J, Kumar M, Oehler C, Ridgway J. Brief report of co-infections with SARS-CoV-2 and other respiratory pathogens. Infect Control Hospi Epidemiol. 2020;1-2. https://doi.org/10.1017/ice.2020.322. Online ahead of print.

Khaddour K, Sikora A, Tahir N, Nepomuceno D, Huang T. Case report: the importance of novel coronavirus disease (COVID-19) and coinfection with other respiratory pathogens in the current pandemic. Am J Trop Med Hyg 2020;00(0):1–2. doi: 10.4269/ajthm.20-0266.

Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of coronavirus disease 2019 and influenza A: a report from Iran. Arch Iran Med 2020;23(4):239–43. doi: 10.34172/aim.2020.04.

Kim D, Quinn J, Pinsky B, Shah N, Brown I. Rates of co-infection between SARS-COV-2 and other respiratory pathogens. JAMA 2020;323(20):2085–6.

Konala V, Adapa S, Gayam V, Naramala S, Daggubati S, Kammari C, et al. Co-infection with Influenza A and COVID-19. Eur J Case Rep Intern Med 2020;7(5) 001656. doi: 10.12890/2020_001656 eCollection 2020.

Lin D, Liu L, Zhang M, Hu Y, Yang Q, guo J, et al. Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected patients. Sci China Life Sci 2020;63(4):606–9. doi: 10.1007/s11427-020-1668-5 Epub 2020 Mar 5.

Ma S, Lai X, Chen Z, Tu S, Qin K. Clinical characteristics of critically ill patients co-infected with SARS-CoV-2 and the influenza virus in Wuhan, China. Int J infect Dis 2020;96:683–7. doi: 10.1016/j.ijid.2020.05.068 Epub 2020 May 26.

Motta J, Gomez C. Adenovirus and novel coronavirus (SARS-CoV2) coinfection: a case report. IDCases 2020;22:e00936.. doi: 10.1016/j.idcr.2020.e00936 Epub 2020 Aug 22.

Nowak M, Sordillo E, Gitman M, Mondolfi A. Co-infection in SARS-CoV-2 infected patients: were are influenza virus and rhino/enterovirus? J of Med Virol. 2020. https://doi.org/10.1002/jmv.25953. Online ahead of print.

Ozaras R, Cirpin R, Duran A, Duman H, Arslan O, Bakcan Y, et al. Influenza and COVID-19 coinfection: report of six cases and review of the literature. J Med Virol. 2020. https://doi.org/10.1002/jmv.26125. Online ahead of print.

Richardson S, Hirsch JS, Narasimhan M, Crawford J, McGinn T, Davidson K,. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA 2020;323(20):2052–9.

Touzard-Romo F, Tape C, Lonks J. Co-infection with SARS-CoV-2 and human metapneumovirus. RI Med J (2013) 2020;103(2):75–6.

U.S. Department of Commerce – Economics and Statistics Administration. U.S. Census Bureau. Census regions and divisions of the United States. 2021. [14th January 2021]. Available https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf.

U.S. Department of Veterans Affairs. Office of rural health. Rural Veterans. [17th August 2020]. Available https://www.ruralhealth.va.gov/aboutus/ruralvets.asp#def.

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.

Wu X, Cai T, Huang X, Yu X, Zhao L, Wang F, et al. Co-infection with SARS-CoV-2 and influenza A virus in patient with pneumonia, China. Emerg Infect Dis. 2020;6(26). doi: 10.3201/eid2606.200299 Original Publication Date: 3/11/2020.

Xie Y, Bowe B, Maddukuri G, Al-Aly Z. Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with COVID-19 and seasonal influenza: a cohort study. BMK 2020;371:m4677. doi: 10.1136/bmj.m4677.

Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B, et al. Co-infection with respiratory pathogens among COVID-2019 cases. Virus Res 2020;285: 198005.