Prevalence of co-infections with respiratory viruses in individuals investigated for SARS-CoV-2 in Ontario, Canada

Running title: SARS-CoV-2 co-infection with respiratory viruses

Key words: SARS-CoV2, co-infection, respiratory viruses, COVID-19

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Abstract (Abstract word count -200)

Background: Co-infections of SARS-CoV-2 with respiratory viruses, bacteria and fungi have been reported to cause a wide range of illness. **Objectives**: We assess the prevalence of co-infection of SARS-CoV-2 with seasonal respiratory viruses, document the respiratory viruses detected among individuals tested for SARS-CoV-2, and describe characteristics of individuals with respiratory virus co-infection detected. **Methods**: Specimens included in this study were submitted as part of routine clinical testing to Public Health Ontario Laboratory from individuals requiring testing for SARS-CoV-2 and/or seasonal respiratory viruses. **Results:** Co-infection was detected in a smaller proportion (2.5%) of individuals with laboratory confirmed SARS-CoV-2 than those with seasonal respiratory viruses (4.3%); this difference was not significant. Individuals with any respiratory virus co-infection were more likely to be younger than 65 years of age and male than those with single respiratory virus infection. Those with SARS-CoV-2 co-infection manifested mostly mild respiratory symptoms.

Conclusions: Findings of this study may not support routine testing for seasonal respiratory viruses among all individuals tested for SARS-CoV-2, as they were rare during the study period nor associated with severe disease. However, testing for seasonal respiratory viruses should be performed in severely ill individuals, in which detection of other respiratory viruses may assist with patient management.

Keywords: co-infection, SARS-CoV-2, Covid-19, seasonal respiratory viruses.

Introduction (Manuscript text word count 3,497)

SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, China, and has progressively spread, resulting in a global pandemic

(1). In Ontario, Canada, the first COVID-19 case was identified on January 22, 2020, with the number of daily cases peaking in the second week of April, during the first pandemic wave (2). As of May 22, 2020, approximately 5 million cases and 300,000 deaths were reported worldwide, including over 80,000 cases and almost 6,000 deaths in Canada (3).

The disease is characterized by a wide range of clinical manifestations, from asymptomatic or mild symptoms (fever, cough, myalgia, and headache) to severe illness (pneumonia, acute respiratory distress, multiple organ failure) and death (4). However, COVID-19 symptoms are non-specific to SARS-COV-2 as they are commonly reported with other respiratory pathogen infections (5-10).

Co-infections of SARS-CoV-2 with respiratory pathogens have been documented previously at varying rates. In a study of 1,101 individuals with respiratory symptoms, in California, co-infection with another respiratory pathogen was reported in 24 (20.4%) of 116 persons with confirmed SARS-CoV-2 (6). The most common secondary viruses identified were enterovirus/rhinonvirus, respiratory syncytial virus (RSV). Another retrospective study of hospitalized children in Wuhan, reported two (1.2%) of 161 children tested positive for co-infection of SARS-CoV-2 with additional viral and/or bacterial respiratory pathogens such as human metapneumovirus [hMPV] and RSV in one child and hMPV and *Mycoplasma pneumoniae* in the second child (7). One of the children was severely ill, requiring intensive care unit (ICU) admission. Co-infections with bacteria and fungi, but not respiratory viruses, were reported among five of 99 severely ill patients in Wuhan (8).

Understanding the epidemiology and prevalence of seasonal respiratory viruses in patients with COVID-19 will help document the rate of SARS-CoV-2 co-infection and better appreciate the

role of such viruses in clinical presentation. This could improve patient management and further contribute to public health practices aimed at virus containment measures.

The objectives of this study were to: assess the prevalence of co-infection of SARS-CoV-2 with seasonal respiratory viruses, document the respiratory viruses detected among individuals tested for SARS-CoV-2, as well as describe characteristics of individuals with co-infection. We also describe and compare characteristics of individuals tested at Ontario's public health laboratory (Public Health Ontario [PHO] Laboratory) for (i) both SARS-CoV-2 and seasonal respiratory viruses (SARS-CoV-2+MRVP) (ii) seasonal respiratory viruses (MRVP) alone.

Methods

This study used a cross-sectional design. Specimens included in the study were submitted as part of routine clinical testing to PHO Laboratory from individuals seen in various hospitals, clinics, and assessment centers across the province. Specimens were tested for SARS-CoV-2 and/or seasonal respiratory viruses. Clinical information was provided on the laboratory requisition by the health care provider. Testing and clinical information was extracted from the laboratory information management system (LIMS) at PHO Laboratory for the period January 11, 2020 to April 20, 2020.

As the pandemic progressed, tests used and associated PHO Laboratory testing algorithms evolved to better address the increased needs and improve turnaround times.

During the study period, testing for SARS-CoV-2 was performed using three different methods: (i) a laboratory-developed endpoint nested polymerase chain reaction (PCR) assay targeting the RNA dependent RNA polymerase (RdRP) gene, followed by Sanger sequencing of amplicons with expected size of approximately 192 base pairs. This assay was adapted from a previously

published Middle East Respiratory Syndrome Coronavirus (MERS-CoV) hemi-nested PCR, but altered such that the relevant primer bases match SARS-CoV-2: an outer primer and newly designed inner primers spanning 192bp were used for both amplification (11); (ii) a laboratory developed real-time reverse-transcription (rRT)-PCR for specific detection of the SARS-CoV-2 envelope (E) gene and RdRp gene (12);(iii) the Roche cobas® SARS-CoV-2 rRT-PCR assay on the cobas® 8800 system, which detects the E gene and open reading frame (orf)1a/b gene. Initial samples were confirmed by the National Microbiology Laboratory (NML) of the Public Health Agency of Canada using a nucleocapsid (N) gene rRT-PCR developed at NML. NML also conducted laboratory developed conventional RT-PCRs targeting RdRp and ORF3a, followed by nucleotide analysis of partial gene sequences of RdRp and ORF3a amplicons. Detection of a single gene by any of the assays was considered positive for SARS-CoV-2. All tests were assessed for cross-reactivity with other respiratory viruses during validation and no-cross reaction was identified.

Testing for seasonal respiratory viruses at PHO Laboratory was performed using a laboratory-developed multiplex respiratory virus PCR assay (MRVP), which detects nine respiratory viruses including: adenovirus, seasonal human coronavirus (229E, NL63, OC43, HKU1), enterovirus, hMPV, parainfluenza (1-4), RSV A/B, rhinovirus, influenza A, influenza A(H3N2), influenza A(pdm09), and influenza B .

From January 11 – March 1, 2020, all respiratory specimens submitted for SARS-CoV-2 testing were also routinely tested for other respiratory viruses. From March 2 - April 20, 2020, testing for non-SARS-CoV-2 respiratory viruses was mainly conducted for inpatient or institutionalized (e.g. long-term care residents, correctional facility inmates) individuals when ordered on the laboratory requisition. Testing was also done for other patients by special arrangement.

Data analyses were performed using Stata SE/10.0. Most analyses were performed at specimen level in order to retain individual's characteristics (patient setting, clinical symptoms and geography) at the time of testing, particularly for those tested multiple times. Duplicate specimens were removed and data were analyzed at the specimen and individual level. Transformation to individual level were conducted only for the key findings.

Descriptive analyses were performed to characterize and compare specimens tested by SARS-CoV-2+MRVP with specimns tested by MRVP alone, with respect to age, gender, patient setting, Ontario health region, outbreak status, and specimen type. Proportion differences between these groups were compared using the chi-square test; a p-value of <0.05 was considered significant. The two groups were also compared with respect to number of respiratory viruses identified.

Viruses identified in each specimen were documented and categorized as: co-infection, single infection or negatives. (i) Co-infection was defined as the presence of SARS-CoV-2 with at least one seasonal respiratory virus or presence of two or more seasonal respiratory viruses in the same specimen; (ii) a single infection was considered when only SARS-CoV-2 or seasonal respiratory virus was detected; (iii) and a negative result was defined as no detection of SARS-CoV-2 and/or seasonal respiratory virus.

The laboratory database was reviewed to identify study specimens that underwent additional molecular testing for the following pathogens: *Legionella* spp. *Bordetella pertussis*, *Mycoplasma pneumoniae* and fungi.

Within the SARS-CoV-2 + MRVP group, symptoms of persons with respiratory viruses detected were assessed by infection category (single infection versus co-infection). Crude and adjusted

logistic regression analyses were performed for samples tested by SARS-CoV-2+MRVP to compare individuals with the likelihood of co-infection versus single infection (the outcome) adjusted for age group, gender, region, patient setting, outbreak related, group of viruses identified (SARS-CoV-2 or seasonal respiratory virus), and specimen type (exposure variables). Odds ratios (ORs) with 95% Confidence Intervals (CIs) were reported and interpreted.

Ethics

The PHO Ethics Review Board has determined that this project did not require research ethics committee approval, as it describes analyses that were completed at PHO Laboratory as part of routine clinical respiratory testing during the first wave of the COVID-19 pandemic in Ontario and are therefore considered public health practice, not research.

Results

From January 11, 2020 to April 20, 2020, 7,225 specimens from 5,228 individuals were tested for both SARS-CoV-2 and seasonal respiratory viruses. A mean of 1.5 specimens, (median 1 specimen; range 1 to 8 specimens) were tested per person. Among individuals with more than one specimen submitted, mean lag time between the first and any subsequent specimen tested was 0.2 days (median 0 days; range 0 to 32 days).

During the same period, 12,421 specimens from 11,542 individuals were tested for seasonal respiratory viruses alone. An average of 1.2 specimens (median 1 specimen; range of 1 to 6 specimens) were tested per person; the mean lag time to subsequent specimen tested was 13 days (median 0 days; range 0 to 86 days).

Individuals tested for SARS-CoV2+MRVP versus MRVP alone differed for all study variables (Table 1). Persons tested for both SARS-CoV-2 and seasonal respiratory viruses were more

likely to be younger (median age 65 versus 70 years), female (56.1% versus 51.6%), tested in an institution (38.8% versus 22.4%) and residing in Toronto (28.5% versus 19.5%) compared to persons tested for seasonal respiratory viruses alone. Additionally, such individuals were less likely to be tested as part of an outbreak investigation (26.3% versus 78.9%);

Of the 7,225 specimens tested by SARS-CoV2+MRVP, 2,210 (30.6%) were positive for at least one respiratory virus compared to 4,152(33.4%) in the group tested by MRVP (n=12,421) alone ($p < 0.001$). Of the specimens tested by SARS-CoV-2 + MRVP, human seasonal coronaviruses 488(6.8%) were the most common viruses detected, followed by SARS-CoV-2 325(4.5%) and rhinovirus 325(4.5%) (Figure 1). Five specimens with SARS-CoV-2+MRVP testing were also tested for *Legionella spp.* and were found to be negative. No other bacterial or fungal testing occurred in our cohort. Of specimens tested by MRVP alone, influenza A 1,166(9.4%) was the most common virus identified followed by human seasonal coronavirus 766(6.8%) and RSV 564(4.5%) (Figure 1). Of influenza A specimens (n=293) detected in the group tested by SARS-CoV-2+MRVP, 231(78.8%) were influenza A/H1N1pdm09 and 46(15.7%) as influenza A/H3N2. Influenza subtype distribution was 83.3% influenza A/H1N1pdm09 and 13.1% influenza A/H3N2 in the group tested by MRVP alone. A small proportion of influenza A specimens (5.5% and 3.6% for each group, respectively) were not subtyped.

Compared to specimens tested by MRVP (n=12,421) alone, those tested by SARS-CoV-2 + MRVP (n=7,225) had fewer viruses detected, whether as a single infection [2,129 (29.5%) versus 3,948 (31.8%)] or co-infection [81 (1.1%) versus 204 (1.6%)] ($p<0.001$) (Table 2). Co-

infection of SARS-CoV-2 with a seasonal respiratory virus was detected in 8/325 (2.5%) of SARS-CoV-2-positive specimens and co-infection of seasonal respiratory viruses was identified in 81/1,893 (4.3%) of specimens with seasonal respiratory viruses detected ($p>0.05$). Of SARS-CoV-2 co-infections, two had seasonal coronavirus, two had rhinovirus, two had RSV, and two had hMPV present. Of seasonal respiratory virus co-infections detected in the specimens tested by SARS-CoV-2+MRVP, influenza A/H1N1pdm09 and rhinovirus (n=8) or adenovirus with seasonal coronavirus (n=5) were the most common co-infections, while influenza A/H1N1pdm09 and seasonal coronavirus (n=24) or RSV with seasonal coronavirus (n=21) in the group tested by MRVP alone.

Characteristics of the eight patients with co-infection involving SARS-CoV-2 and a seasonal respiratory virus are shown in Table 3. The age of persons with SARS-CoV-2 co-infection was between 50-91 years (median age 75 years) and six were male. Fever and cough were the most common symptoms reported.

Symptoms of persons with respiratory viruses detected among patients tested by SARS-CoV-2 + MRVP by infection category (single infection versus co-infection) are presented in Figure 2. The three most common symptoms reported by both patients with SARS-COV-2 (n=325) identified or seasonal respiratory viruses (n=1,893), whether as single infection or co-infection, were fever, cough and undefined respiratory symptoms. Specifically, among SARS-CoV-2 groups of single infection (n=317) versus co-infection (n=8), the number and proportion with reported fever were 164 (51.7%) versus 2 (25.0%), undefined respiratory symptoms 122 (38.5%) versus 4 (50.0%), and cough 91 (28.7%) versus 3 (37.5%). For the respective groups of seasonal respiratory viruses (single infection n=1,812 versus co-infection n=81), number and

proportions of reported fever were: 808 (44.6%) versus 28 (34.6%); undefined respiratory symptoms 665 (36.7%) versus 48 (59.3%); and cough 936 (51.7%) versus 39 (48.1%).

In the adjusted logistic regression analyses (Table 4), persons < 65 years of age had significantly higher odds of being diagnosed with viral co-infection compared to single infection [OR=3.1 and 95% CI (1.5-6.2)]; the odds of being diagnosed with co-infection were 60% higher for males in comparison to females [OR=1.6;95% CI (1.0-2.5)]. The odds of having a SARS-CoV-2 co-infection with another seasonal respiratory virus were lower than the odds for co-infection between two seasonal respiratory viruses; however, this difference was not significant.

Discussion

In this study we describe testing for SARS-CoV-2 and/or seasonal respiratory viruses at PHO Laboratory, Ontario's reference microbiology laboratory. Persons tested for both SARS-CoV-2 and seasonal respiratory viruses were slightly younger than patients tested for seasonal respiratory viruses alone. This is likely because most individuals tested for seasonal respiratory viruses alone were tested as part of provincial outbreak investigations, representing mostly older adults residing in retirement homes and long term care facilities. Early in the pandemic, SARS-CoV-2 testing was not routinely done in retirement homes and long term care facilities, since at this time no virus was circulating in such settings. Individuals tested for SARS-CoV-2 and seasonal respiratory viruses were predominantly females, which is likely driven by SARS-CoV-2 testing. This is similar to findings in a provincial report describing characteristics of SARS-CoV-2 cases in Ontario (2).

Individuals tested for SARS-CoV-2 and seasonal respiratory viruses were seen mainly in ER and institutions. This could represent testing patterns for SARS-CoV-2 at the time, targeting

mostly travel related cases presenting to emergency rooms (ER) in the beginning of the pandemic, moving later towards broader criteria, including outbreaks in institutions. Those who were tested for seasonal respiratory viruses alone mostly received care in hospital. PHO Laboratory routinely only accepts specimens for respiratory virus testing from inpatients, institutionalized persons and those affected by respiratory outbreaks. Testing for respiratory viruses is not usually performed for patients seen in ambulatory/outpatient settings, or those seen in ER, though it is provided on special request (13).

Individuals tested for SARS-CoV-2 and seasonal respiratory viruses at PHO Laboratory were most likely from the Toronto area in comparison to those tested for respiratory viruses alone being from Central East Ontario. This resembles the population for which PHO Laboratory serviced, with SARS-CoV-2 testing in Ontario moving from centralized testing at PHO Laboratory in Toronto, in the beginning of the pandemic, to more distributed testing across other provincial hospitals and private laboratories as the pandemic progressed. Furthermore, as other laboratories implemented SARS-CoV-2 testing, they shifted from forwarding specimens to PHO Laboratory for both SARS-CoV-2 and seasonal respiratory virus testing to ordering seasonal respiratory virus testing only.

While the same respiratory viruses were detected in both groups, percent positivity for at least one respiratory virus was 30.6% in the group tested for both SARS-CoV-2 and seasonal respiratory viruses and 33.4% in the group tested for respiratory viruses only. Seasonal coronavirus was the most common virus detected in the first group and influenza A in the second one. This could be reflective of more specimens being tested for seasonal respiratory viruses early before SARS-CoV-2 fully evolved, which corresponds to the peak of influenza season in

Ontario. These two viruses were also the most common circulating viruses in Ontario at that time (14).

Co-infection with two or more respiratory viruses was detected in 1.1% of specimens tested for both SARS-CoV-2 and seasonal respiratory viruses and in 1.6% of specimens tested for respiratory viruses alone, with the most common being influenza A(H1N1)pdm09/ rhinovirus and adenovirus/seasonal coronavirus in the first group, and influenza A(H1N1)pdm09/ seasonal coronavirus and respiratory syncytial virus/seasonal coronavirus in the second group. Interestingly, percent positivity and percent of co-infections in this study were much lower compared to previously reported data in a community- acquired respiratory viruses co-infection among patients of sentinel practices network (SPSN) in Ontario, Canada (15). In this study, at least one respiratory virus was identified among 65.6% of individuals and co-infection in 15.3% of tested individuals (15). Results were lower in our study for two main reasons: first, unlike the SPSN study, we did not have any clinical enrollment requirements for patients being included in our study; secondly our study period included only the first four months of COVID-19 pandemic, limiting ability to capture several seasonal viruses such as enterovirus and rhinovirus, which typically circulate in summer - fall. Even influenza virus was not fully captured in our study, as influenza season had already peaked in Ontario when the COVID-19 pandemic started (14). Decrease in influenza activity was also reported following onset of the CoVID-19 pandemic, likely due to mitigation strategies put in place to reduce the spread of SARS-CoV-2 virus (16). All of these factors combined may led to both an underestimation and reduction in season respiratory infection identified in this study, including co-infection.

This study found co-infection of SARS-CoV-2 with seasonal respiratory virus in 2.5% of SARS-CoV-2 positive specimens. Several studies investigating SARS-CoV-2 co-infection have

reported varying rates of co-infection (4, 5-8, 17-24). Wang et al followed 8,274 close contacts of COVID-19 cases in a university hospital in Wuhan, China and found co-infection with respiratory viruses in 5.8% of 2,745 patients with laboratory confirmed SARS-CoV-2 (17). Conversely, a retrospective study among 257 positive laboratory-confirmed SARS-CoV-2 cases, screened patients during hospital admission for 39 respiratory pathogens and found co-infection in 243 (94.2%) of individuals with either respiratory viruses (31.5%), bacteria (91.8%) and fungi (23.3%) (18). Although some of these co-infections were likely colonization, most of them were documented within 1-4 days of COVID-19 disease onset, and individuals with SARS-CoV-2 had the most severe disease. The main reasons for differences in reported co-infection rates between studies rely on the population being investigated, the study period, testing methods used to identify secondary pathogens, and spectrum of secondary pathogens targeted.

We found being younger than 65 years of age and male increased risk of co-infection. Similarly, Zhu et al. reported higher rates of co-infection among the 15-64 year old age group than those 65+ and children <15 years of age, but no differences in co-infection between females and males. Of note, their results were not adjusted for all variables in the study (18). In our study, co-infection was neither that common nor significantly different for those with confirmed SARS-CoV-2 (2.5%) and those with seasonal respiratory viruses (4.3%). A systematic review had similar findings - prevalence of COVID-19 co-infection with another respiratory virus was reported to be 3%, with RSV and influenza A most common (25). Co-infection could depend on season and also on the pathogenic competition between viruses as the risk of testing positive for SARS-CoV-2 was previously reported to be 58% lower among influenza positive cases (26).

In our study, persons with SARS-CoV-2 co-infection mostly reported mild respiratory symptoms including fever, cough and undefined respiratory symptoms. Apart from evidence that

two of these individuals were seen in ER, there was no clear indication of disease severity. Being tested as part of an outbreak investigation and receiving care in an institution would indicate that the other six patients were likely elderly, and therefore at risk for more severe respiratory disease. However, disease severity cannot definitively be established. SARS-CoV-2 co-infection with bacteria or fungi rather than respiratory viruses are reported to be potentially lethal in ICU patients (24). A higher risk of death among individuals with SARS-CoV-2 and influenza co-infection than those with SARS-CoV-2 alone was previously reported (26). These findings highlight the importance of considering testing for other respiratory pathogens (bacteria, viruses and fungi), particularly in critically ill COVID-19 patients. To our knowledge, testing for other bacterial and fungal respiratory pathogens was rarely done in our cohort. Considering that 69.3% of specimens tested negative for SARS-CoV-2 or seasonal respiratory virus, it is important to investigate other causes that may be part of the differential.

Limitations

There are several limitations in this study. First, our study included individuals who received testing at PHO Laboratory and therefore is not representative of all individuals tested in Ontario. Second, not all specimens tested for SARS-CoV-2 underwent testing for seasonal respiratory viruses. This would have limited the detection of the full spectrum of seasonal respiratory viruses present and underestimated co-infection. Third, testing methods for SARS-CoV-2 virus changed over time to fit pandemic needs. Differences in sensitivity and specificity between tests may exist, which may have caused some missed diagnoses in SARS-CoV-2 cases and consequently fewer co-infection detections. Fourth, as a reference microbiology laboratory, PHO Laboratory does not perform primary bacteriology on respiratory specimens except for *Legionella* species, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. In addition, testing for bacterial and

fungal pathogens were not broadly requested; therefore we could not adequately examine co-infection of SARS-CoV-2 with bacteria or fungi. Lastly, PHO Laboratory does not have access to patient care charts, and relies on clinical information provided on the laboratory requisition, which may not be fully reliable.

Conclusions

Co-infection was detected in a smaller proportion (2.5%) of individuals with laboratory confirmed SARS-CoV-2 infection than in individuals with seasonal respiratory viruses (4.3%); however this difference was not significant. Individuals with any respiratory virus co-infection compared to those with single respiratory virus were more likely to be younger than 65 years of age and male. Those with SARS-CoV-2 co-infection manifested mostly mild respiratory symptoms, such as fever and cough, which was similar to patients with single respiratory virus infection.

In summary, findings of this study may not support routine testing for seasonal respiratory viruses among all individuals tested for SARS-CoV-2, as they were not commonly found during the study period nor clearly associated with severe disease. However, testing for seasonal respiratory viruses should be performed in severely ill individuals, in which detection of other respiratory viruses may assist with patient management.

Footnote page

Conflict of interest

None declared.

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