The Complexity of Co-Infections in the Era of COVID-19

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Abstract

The current frequency of COVID-19 in a pandemic era ensures that co-infections with a variety of co-pathogens will occur. Generally, there is a low rate of bonafide co-infections in early COVID-19 pulmonary infection as currently appreciated. Reports of high co-infection rates must be tempered by limitations in current diagnostic methods since amplification technologies do not necessarily confirm live pathogen and may be subject to considerable laboratory variation. Some laboratory methods may not exclude commensal microbes. Concurrent serodiagnoses have long been of concern for accuracy in these contexts. Presumed virus co-infections are not specific to COVID-19. The association of influenza viruses and SARS-CoV-2 in co-infection has been considerably variable during influenza season. Other respiratory virus co-infections have generally occurred in less than 10% of COVID-19 patients. Early COVID-19 disease is more commonly associated with bacterial co-pathogens that typically represent usual respiratory micro-organisms. Late infections, especially among severe clinical presentations, are more likely to be associated with nosocomial or opportunistic pathogens given the influence of treatments that can include antibiotics, antivirals, immunomodulating agents, blood products, immunotherapy, steroids, and invasive procedures. As for other viral infections, a general reduction in the use of empiric antibiotic treatment is warranted. Further insight into co-infections with COVID-19 will contribute overall to effective antimicrobial therapies and disease control.

Keywords COVID-19 · Coronavirus · Co-infection · Diagnosis

Introduction

The pandemic of SARS-CoV-2 infection carries with it many nuances regarding epidemiology, microbiology, and clinical manifestations. With intense focus on treatment and prevention, proportionately less weight has been given to understand this virus in the milieu of other human pathogens that may co-exist or complicate infections. As for other serious or prolonged respiratory virus infections, it is inevitable that other pathogens will complicate clinical presentations, active disease, diagnostics, and surveillance. This narrative review examines various aspects of COVID-19 co-infection and illustrates key lessons that are either newly apparent or simply re-learned but highly relevant.
potential overlap provides credence for the existence of true co-infections or infections superimposed on a previous virus disease.

The vast array of respiratory viral pathogens, and especially in more contagious circumstances such as winter season, school, childhood care, and highly populated co-habitations, ensures that there is plenty of opportunity for co-detctions. Co-detctions, however, do not always equate with co-infection, and it may at times be quite evident that two proximal clinical infections have occurred in sequence. Residual pathology from the first infection may affect the likelihood, frequency, and/or nature of the disease that arises when the next pathogen emerges. Patient co-morbidities have the potential to influence outcomes. Following from the latter, co-infections may emerge from pathogens that naturally complicate viral infections such as normally resident respiratory bacteria. These may include an enrichment of, or pre-selection for, bacteria or fungi that proliferate during disease or with proc-livy to compromise antibiotic treatments or immunologically susceptible patients. In this regard, it would be anticipated that nosocomial infection should complicate COVID-19 as for other viral respiratory infections. The contamination of clinical samples with usual respiratory micro-organisms must be considered in sophisticated analyses [1].

There are many anecdotes of prolonged human endemic coronavirus shedding [2, 3]. Many of these findings are based on non-culture methods and detect viral genome only. Therefore, the concept that such detection may be prolonged when indeed another virus or other pathogen arises is evident.

A collection of studies also find live SARS-CoV-2 excretion well after 10 days, but in the minority [4]. Very prolonged genome shedding as well as anecdotes which find live virus as late as 102 days after disease onset have been detailed [5].

**Diagnostic Quandaries**

There are many technical difficulties that may arise in defining diagnoses for co-infections (Table 1). Most findings of coronavirus in clinical samples depend on RNA amplification strategies, and these do not discriminate live and potentially infectious virus from inactive residual virus. Virus may therefore be detected in the presymptomatic state, active infection, or short or prolonged post-infectious resolution [6]. Most of-ten, the context for co-detection will be an active infection whereby the co-pathogen(s) identified is/are from the tail end of excretion due to preceding infection. Many studies of co-virus infection have not used secondary methods to con-firm coronavirus detection let alone other viruses [2]. An example of the potential magnitude of this issue is illustrated by the finding in one study of a viral co-pathogen in 96% of coronavirus detections [7]. It should be emphasized that co-detection or co-diagnosis otherwise does not always amount to co-infection.

Positive indices for genome amplification detection are set at a given standard, and in the absence of confirmatory alternate or repeat testing, they may be relatively arbitrary. There is potential for both under- or over-diagnosis. An adjustment of methodological thresholds can pit sensitivity against specific-ity. The findings of a high frequency of putative co-infections or the presence of multiple co-existing viral or atypical pathogens should alert the observer to such diagnostic complexity. Variation in methods and diagnostic thresholds also exists between laboratories, thus complicating comparisons. Partial genome amplification technologies can allow for an estimate of coronavirus quantitation, i.e., low thresholds of detection may equate with greater viral load presence. Coronavirus quantitations as estimated by amplification methods were higher for symptomatic patients, and, in two studies, when the coronavirus was the only virus found in samples in con-trast to co-infections [8, 9]. In the work of van der Hoek et al. [10], human endemic respiratory coronavirus NL63 was present in a significantly higher viral load from samples where this virus was identified alone in contrast to those samples where it was found in putative co-infections. In another study, there was no correlation of viral load with severity [11].

In addition, non-genetic amplification diagnostic methods also have their potential foibles. Diagnostic serology has long been cautiously applied in epidemiological studies. Dependence on IgM serology in particular has raised issues with non-specificity. Detection of viral antigen through immunoassay or through direct immunofluorescence assays can also be susceptible to sensitivity or observer technological limitations. For example, viral antigen detection is of greater sen-sitivity when the infection is at a peak and when viral quanti-tation is near its peak.

**The Example of Putative *Mycoplasma pneumoniae* Co-Infection with SARS-CoV-2**

True co-infections with *M. pneumoniae* will inevitably occur due to the frequency of the bacterium as a common cause of community-acquired respiratory infection in children and relatively young adults throughout the world [12]. Several publications detail possible co-infections for SARS-CoV-2 and *M. pneumoniae* [13–22]. There are several methodological issues arising however which complicate the validity and applications (Table 2). The large tally of such infections in one COVID-19 cohort seems unlikely however to represent bonafide co-infection [13]. The latter reported that over one-half of COVID-19 infections admitted to hospital were sero-positive for *M. pneumoniae*-IgM. The latter frequency of *M. pneumoniae* is generally not seen even in epidemics of the same bacterial infection. The reliance on IgM serology alone could explain a high false-positive rate. Some patients had two
co-pathogen detections, and one patient was said to have SARS-CoV-2 along with four co-pathogens. The lack of an IgG response to co-exist in some reports, even early, is unlikely since IgG reactivity occurs alongside or very shortly after IgM detection for *M. pneumoniae*. In one citation and examining paired sera over 15 days, the patient’s IgM response disappeared as did the IgG response [17]. Anti-*M. pneumoniae* IgM responses rise usually within 7 days or more after infection onset, and the subsequent IgG responses along with IgM are likely to persist for weeks to months thereafter [23]. One must realize that *M. pneumoniae* serology could be either non-specific or that *M. pneumoniae* infection occurred much earlier than COVID-19, and that the serological response was yet lingering.

Atypical pneumonia presentations from *M. pneumoniae* can confuse with clinical diagnoses of COVID-19. Conventional serological diagnosis for *M. pneumoniae* can be fraught with difficulty unless confirmed with immunoblotting [23, 24]. Non-specific polyclonal activations for rheumatoid factor or other antibodies can also arise [25]. Rheumatoid factor is a well-recognized potential confounder for IgM serology. The phenomenon of potential overdiagnosis is illustrated by the manner in which cumulative data can be skewed by unrecognized diagnostic difficulties for *M. pneumoniae* [26]. These features would generally parallel expectations and concerns for other putative co-infections.

Of note in the above regards, Fujita illustrates how *M. pneumoniae*, like some respiratory viruses, has diminished in prevalence during the time when enhanced precautions are being observed for SARS-CoV-2 [27]. The high frequency of *M. pneumoniae* infection in the midst of other virus infections has been proposed both recently and in the past many times [28].

### Lessons From Comparative Human Coronavirology and Co-Infection

Prior to SARS-CoV-2, there were many population studies throughout the world that detailed the frequency of endemic respiratory human coronaviruses and their associations with co-infection [2]. Several commonalities emerged. In a context where these endemic coronaviruses comprised a considerable minority of causative agents for community-acquired respiratory infections, the frequency of co-infection was quite variable but at times as frequent as three-fourths of the entirety. Multiple co-viral pathogens were sometimes detected, and several reports documented presence of more than one co-existing coronavirus in a clinical sample. Common viral co-pathogens included respiratory syncytial virus, rhinovirus, influenza, and adenovirus, and there was no bias for any one of the four endemic respiratory coronaviruses being associated with co-infection.

The finding of the above coronaviruses in co-infection did not consistently associate with worse outcome, type of illness, or age groups with some exceptions [2, 29]. Few studies validated co-infections with secondary confirmatory diagnostics which raises concern for specificity [2, 30]. Of equal importance, some studies found equal frequency of viral co-infections regardless of whether the respiratory coronavirus detection occurred for ill patients or asymptomatic controls [9, 31]. At least in this context, the finding of co-detections raises concern of whether the observations are truly indicative of co-infections even if such chance observations are to be anticipated. These issues are only more so suspect given that the majority of reports used genome amplification technologies only for coronavirus and other virus detections.

There are comparatively few reports of co-infections among patients who suffered Severe Acute Respiratory

### Table 1 General technical problems potentially associated with the diagnosis of co-infections

| A | Variable diagnostic thresholds with RT-PCR for SARS-CoV-2 or other potential pathogens. |
| B | Variable diagnostic targets for PCR or RT-PCR. |
| C | Prolonged amplification test positivity in the absence of viable pathogen. |
| D | Asymptomatic infection. |
| E | Changes in resident upper respiratory tract bacteria after viral infection onset. |
| F | Reliance on molecular assays rather than inclusion of standard culture and microscopy. |
| G | Contamination of clinical samples with oropharyngeal bacteria. |
| H | Lack of confirmatory diagnostic tests. |
| I | Reliance on serodiagnosis alone. |
| J | Potential non-specificity of IgM immunodiagnostics. |
| K | Non-specific polyclonal immune cell activations with infection onset. |
| L | Applying serodiagnostic methods in low prevalence situations. |
| M | Case definition with varying predictive values. |
| N | Variation in quality of diagnostic samples. |
| O | Colonization of the lower respiratory tract during mechanical ventilation without active infection. |
Infection (SARS) or Middle East Respiratory Syndrome (MERS). Lee and colleagues [32] found a high rate (20%) of co-incident human metapneumovirus infections among SARS patients. SARS illnesses did not seem to be complicated by the second virus. No confirmatory studies were performed. The finding of co-pathogens with MERS is complicated by the lack of finding MERS among large groups of patients in many studies [33–35]. A small study of 47 MERS infections did not find co-viral pathogens [36]. Co-infections of MERS-CoV with tuberculosis and influenza have only emerged with few patients [37, 38].

The COVID-19 Experience

Co-Detection of SARS-CoV-2 and Influenza Virus

An animal model of SARS-CoV-2 infection has been used to study co-infection with an influenza H1N1 variant [39]. Co-infection or sequential infection was associated with an accentuation of lung pathology.

Several reports of co-infection with influenza were obtained after the first wave of COVID-19 in early 2020 [19, 40–46]. Four reports from China detailed a high frequency of influenza co-infection, especially for influenza A variants [19, 42, 43, 46]. The finding of nearly one-half of their patients having dual infection raises some concern for diagnostic specificity. These studies utilized IgM immunofluorescence or EIA serology for influenza diagnosis without secondary tests of confirmation. Other analyses from some of these studies suggested that certain co-infections could have correlates with poor overall outcomes. Yet another publication determined a very high frequency of co-infection among patients who deceased [41]. Using genome amplification diagnostic methods, both influenza and other respiratory virus co-infections were considerably frequent (~47%). The study also highlighted co-infections among children where the second virus was solely human metapneumovirus. This study too raises concern about the specificity of laboratory viral diagnostics when a single method for determination is utilized. As has been experienced globally, control measures for COVID-19 have necessarily led to a considerable decline in other virus infections including influenza [45, 47, 48]. Yu et al. [44] further detail the possible effect of antiviral therapy to mitigate dual infections where influenza is seemingly a co-factor. The frequency for finding influenza has been exceedingly low in some centers [47, 49–51]. Further reduction may be linked to COVID-19 public health precautions [27].
Co-Detection of SARS-CoV-2 and Other Respiratory Viruses

Table 3 illustrates the spectrum of viral co-detections that have been found among COVID-19 patients. Several themes emerge. Generally, the co-infection frequency with other viral pathogens is low [47, 58, 61, 63, 67–69, 74–78]. One systematic review identified a relatively low incidence of viral co-infection (~3%) [26]. The large multicenter cohort study from MI, USA found only a 0.5% incidence of viral co-infection when samples were obtained in early presentations [76]. Co-virus patterns of laboratory diagnostics do not in themselves associate with COVID-19 [55, 62]. Among the more common seemingly co-virus pathogens are rhinovirus/enterovirus, respiratory syncytial virus, and influenza viruses. Most of these studies are observational and vary in the spectrum of other viruses that could be detected. Apart from SARS-CoV-2, other coronaviruses have been co-detected, but not any one has a predilection for such association [44, 47, 52, 54, 56, 62, 71–73, 79]. Some co-infections have included more than one other virus [18, 56, 57, 62, 71]. Among deceased patients, there is a greater frequency of co-infections, especially influenza, in early reports [41, 42]. The frequency of co-finding human metapneumovirus did not change before and after the pandemic onset [80]. Most putative co-infections are mild in presentation and convalescence [52]. Nevertheless, some reports suggest that co-infection may be associated with a higher rate of intensive care requirement or prolonged hospital stay [53, 66, 78]. Viral co-infection does not seem to be correlated with age [54]. The citation of SARS-CoV-2 and MERS-CoV co-infections must be carefully considered for diagnostic thresholds and confirmatory testing [79].

Despite the above, it has been noted by many that a general reduction in the prevalence of other seasonal respiratory viruses has been evident and has been ascribed to prevention measures otherwise used for COVID-19 [81, 82].

Co-Detection of SARS-CoV-2 with Selected Non-Viral Infections and Chronic Viral Infections

There are many anecdotes of co-infection that include a very broad array of human pathogens, and there are yet likely many more examples to come if not only for the co-incidence that they should occur. Given the global reality of the pandemic, and regardless of seasonality, co-infections are seen among patients with unique non-viral infections. Reports have been made of SARS-CoV-2 infection complicating parasitic diseases [83–85]. Intestinal parasite co-infection however was seemingly associated with less severe COVID-19 [86]. Yet other reports illustrate virus infection either complicating or giving way to various fungal infections [87, 88]. With the use of multiple antibacterial treatments, corticosteroids, or immunomodulating agents otherwise, it is not surprising to see an association of COVID-19 with opportunistic fungi such as yeast and *Aspergillus* spp. among others [88–92]. The importance of appropriate case definitions for infection is underscored [91, 93]. Unique co-infections with atypical or chronic bacterial infections (in addition to *M. pneumoniae* as previously discussed) have also been cited [94–100]. Among the latter, the finding of 20% of adults having concomitant *Bordetella pertussis* infections must raise again concern with the applicability of diagnostic methods [100]. For *Clostridium difficile*, associated risk factors for co-infection including antibiotic use are not surprising, and there is no seemingly unique propensity with COVID-19 [99].

There are citations of unique co-infections of SARS-CoV-2 with other systemic viral illnesses [101–111]. Such co-infection was particularly of interest in the context of chronic HIV infection where persistent immunocompromise or enhanced infection susceptibility otherwise might allow for either of the infections to be more severe than not [104–106, 112]. HIV-1 co-infection is associated with altered T cell responses to SARS-CoV-2, and this phenomenon was also observed for *Mycobacterium tuberculosis* co-infections [110]. Others have found some contradictory evidence [113]. These studies do not, however, indicate that either of the latter infections markedly affects the other. For chronic hepatitis B patients, early reports suggest that COVID-19 increases the potential for complicating outcomes [107, 108]. Others have suggested that chronic hepatitis B did not predispose patients to a more severe outcome [109]. In the context of chronic hepatitis C infection, COVID-19 did not appear to occur more often nor was it associated with overly severe outcomes [114]. Reactivation of systemic herpesvirus group infections should be reconsidered when severely ill COVID-19 patients are cared for [111].

The Impact of COVID-19 on Associated Post-Onset Bacterial Infections

Virus upper respiratory infections are commonly associated with a quantitative increase in various normal commensal bacteria. The latter phenomenon increases the odds of secondary bacterial infections of the middle ears, sinuses, and respiratory tract in the milieu of existing viral-induced inflammation. The occurrence of secondary infections is generally anticipated, albeit the frequency of the same could be variable. Such perturbation is also evident during COVID-19 as shown through molecular epidemiological studies of the upper respiratory microbiome [115–117]. Admission to healthcare centers carries with it the opportunity for nosocomial infections. Again, these should occur to some degree given the potential severity and prolonged hospital stay for some COVID-19 infections. Respiratory and bloodstream infections are among the more common nosocomial infections [118]. Empiric, potent, or prolonged antibiotic therapy increases risk for
Table 3  Studies of SARS-CoV-2 co-infections associated with other respiratory viruses in varied populations. (a – Total Sample may refer either to total clinical respiratory samples acquired or total SARS-CoV-2 infected patients sampled; b – denotes whether a secondary test was applied which could provide confirmatory information to the initial laboratory diagnostic measure; rCoV = endemic human respiratory coronavirus; RSV = respiratory syncytial virus; RV = rhinovirus/enterovirus; InfA/B = influenza A or B; para = parainfluenza virus; Ad = adenovirus; hMpv = human metapneumovirus; hBoc = human bocavirus; other = included Epstein-Barr virus, herpes simplex, and cytomegalovirus; “= 0 or not determined; RT-PCR = reverse transcriptase polymerase chain reaction; DFA = direct immunofluorescence)

| Geography          | Population                | Total Sample | Frequency overall | rCoV | RSV | RV | InfA/B | Para | Ad | hMpv | hBoc | other | Test method         | Confirmation b | Reference |
|--------------------|---------------------------|--------------|-------------------|------|-----|-----|--------|------|----|------|------|-------|---------------------|----------------|----------|
| Qingdao/Wuhan, China | Pediatric                 | 34           | 14.7%             | -    | 2   | 2   | -      | -    |    | -    | -    | 5     | RT-PCR              | Two independent labs | [18]      |
| Wuhan, China       | Pediatric                 | 81           | 6 (7.4%)          | 1    | 3   | 1   | 1      | 1    |    | -    | -    | -     | DFA                 | None            | [22]      |
| Iran               | All ages, deceased        | 105          | 49 (46.7%)        | 8    | 23  | 4   | 2      | 3    | 9  | -    | -    | -     | RT-PCR              | None            | [41]      |
| Wuhan, China       | Adult, critical illness   | 93           | 47 (49.5%)        | -    | -   | -   | 46     | 1    | 1  | -    | -    | -     | RT-PCR, IgM serology| None            | [42]      |
| Australia          | All ages                  | 92           | 7 (7.6%)          | -    | 5   | 2   | -      | -    |    | -    | -    | -     | Sequencing          | Two methods     | [50]      |
| Jeddah, Saudi Arabia | Not detailed              | 35           | 2 (5.7%)          | -    | -   | 2   | -      | -    |    | -    | -    | -     | Sequencing          | None            | [51]      |
| Singapore          | Not detailed              | 431          | 6 (1.4%)          | 1    | 3   | 2   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [52]      |
| Chicago, USA       | Adult                     | 291          | 5 (1.7%)          | -    | -   | 2   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [53]      |
| North California, USA | All ages                  | 116          | 20.1%             | 5    | 6   | 8   | 1      | 3    |    | -    | -    | -     | RT-PCR              | None            | [54]      |
| Chicago, USA       | Pediatric                 | 101          | 2.0%              | -    | 1   | 1   | -      | -    |    | -    | -    | -     | RT-PCR (only RSV and InfA/B) | None            | [55]      |
| Chicago, USA       | Not detailed              | 459          | 3.3%              | 1    | 8   | 3   | 1      | 2    | 2  | -    | -    | -     | RT-PCR              | None            | [56]      |
| Shenzhen, China    | All ages                  | 92           | 6.5%              | 2    | 3   | 2   | -      | 1    |    | -    | 2    | -     | RT-PCR              | None            | [57]      |
| San Francisco, USA | Adult                     | 33           | 0%                | -    | -   | -   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [58]      |
| New York, USA      | All ages                  | 1996         | 3 (2.0%)          | 7    | 4   | 22  | 1      | 3    |    | 2    | -    | -     | Not detailed         | Not detailed    | [59]      |
| Paris, France      | All ages                  | 301          | 21 (6.6%)         | 6    | 4   | 5   | 3      | 4    |    | -    | -    | -     | RT-PCR              | None            | [60]      |
| Shanghai, China    | Ages ≥ 15 yrs.            | 89           | 0%                | -    | -   | -   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [61]      |
| Hershey, USA       | All ages                  | 148          | 6.1%              | -    | -   | -   | -      | -    |    | -    | -    | -     | Not detailed         | Not detailed    | [62]      |
| Atlanta, USA       | Not detailed              | 31           | 0%                | -    | -   | -   | -      | -    |    | -    | -    | -     | RT-PCR              | Metagenomic sequencing | [63]      |
| Iran               | All ages, deceased        | 74           | 39 (52.7%)        | 6    | 20  | 2   | 2      | 3    | 6  | -    | -    | -     | RT-PCR              | None            | [64]      |
| San Diego, USA     | Adult                     | 51           | 1 (2.0%)          | -    | -   | 1   | -      | -    |    | -    | -    | -     | RT-PCR, antigen detection | None            | [65]      |
| Wuhan, China       | Adult                     | 250          | 18 (7.2%)         | -    | 12  | 3   | 7      | -    |    | -    | -    | -     | RT-PCR, IgM serology | None            | [66]      |
| Chengdu, China     | Adult                     | 24           | 1 (4.2%)          | -    | -   | -   | 1      | -    |    | -    | -    | -     | RT-PCR              | None            | [67]      |
| Basel, Switzerland | All ages                  | 309          | 5.5%              | 5    | 1   | 7   | 2      | 4    | 1  | -    | -    | -     | RT-PCR              | None            | [68]      |
| Barcelona, Spain   | Adult                     | 251          | 7 (2.8%)          | -    | 1   | 6   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [69]      |
| Jiangsu province, China | All ages                  | 257          | 94 (36.6%)        | -    | 12  | 7   | 1      | 10   | 1  | 1    | 63   | -     | RT-PCR              | None            | [70]      |
| Guangzhou, China   | Adult                     | 32           | 15.6%             | 2    | 1   | 1   | 1      | 1    |    | -    | -    | 1     | RT-PCR              | None            | [71]      |
| Reunion Island, France | Adult                    | 36           | 2 (5.5%)          | 1    | -   | 1   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [72]      |
| Ontario, Canada    | All ages                  | 325          | 8 (2.5%)          | 2    | 2   | 2   | -      | 2    |    | -    | -    | -     | RT-PCR              | With or without sequencing | [73]      |
| Baltimore and Washington DC, USA | Adult                  | 1016         | 2 (0.2%)          | 1    | 1   | -   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [74]      |
| Torino, Italy      | Adult                     | 10           | 0                 | -    | -   | -   | -      | -    |    | -    | -    | -     | RT-PCR              | None            | [75]      |
nosocomial infection. In addition, the COVID-19 context has been significantly associated with increasing antibiotic use [119–121]. The presence of a potentially complex infection along with the use of either steroids or immunomodulatory treatments otherwise increases the potential for secondary bacterial infections. The respiratory microbiome is anticipated to change during the course of infection [122]. More severe illnesses will increase the propensity to use invasive treatment and monitoring if not mechanical ventilation and hence again increase the tendency for secondary bacterial infections. Patient co-morbidities will also be anticipated to affect secondary infection rates. Perez et al. [123] found that reluctant or inadvertent relaxation of infection control policies during intense COVID-19 activity might account for such nosocomial infections. Others found evidence of relapsing Gram-negative nosocomial infections as pandemic disease emerged in the context of focused infection control measures [124].

The detection of bacterial co-pathogens does not ensure cause-and-effect relationship. As for co-viral infections, co-detection does not consistently imply co-infection. Some patients may have carriage of high numbers of potentially pathogenic bacteria in either the respiratory tract or at the endotracheal site during intubation without infection. The potential for such ambiguity is illustrated by several studies in which molecular amplification studies have been used for secondary bacterial diagnosis [100, 125–129]. Although there is a correlation of amplification Ct values with bacterial load, even such quantitative assessment does not necessarily imply infection. Furthermore, such detection does not guarantee live bacterium analogous to the issue of viable versus non-viable virus with similar technology. Kolenda et al. [129] tactfully address this issue with corroborative evidence. They found that up to 60% of bacteria found by amplification assay could not be corroborated with culture results. A majority of such determinations were of usual normal oral bacteria and of lesser numbers. What is lost in these approaches is the art of correlation between microscopic smear examination and semi-quantitative bacteriology which often can give strong clues to the validity of data application [130]. Using microscopic smear examination of good quality respiratory samples may also allow the finding of a predominance of white blood cells which are mononuclear in morphology and which may further the likelihood of virus or atypical agent versus usual cultivable bacteria. The potential lost art of microscopy in this context cannot be underestimated.

The COVID-19 experience on this theme is considerable to date. Empiric antibiotic use is common among these patients [76, 119–121, 131]. The frequency of such use may decline with experience [76]. Macrolide and beta-lactam antimicrobial use dominate in this context [121]. There is a low incidence of secondary bacterial infections in many studies [74, 76, 120, 121, 131–134]. The lower incidence is most common among the very early phases of infection as would be anticipated [76, 134]. The type of proposed co-pathogen changes during the course of COVID-19 [49, 76, 118, 128, 134–140]. Common respiratory bacteria more often cause infection in early stages of the illness [75, 125, 129, 133, 141–143]. Nosocomial infections can be common as the viral illness progresses albeit the institutional rate is quite variable [49, 118, 119, 123, 131, 135–140, 144–147]. Much of the latter includes opportunistic Gram-negative bacilli [49, 100, 118, 119, 123, 124, 126, 137, 138, 140, 144, 145, 147, 149–151]. Fungal infections, especially with Candida spp., occur with worse disease and increased hospital stay [118, 126, 135, 136, 139, 144, 145, 147, 149–151]. The latter may occur in up to 14% of such patients [134, 138, 139]. As anticipated, antimicrobial therapy and steroid use can pose as risk factors for such invasive fungal infections [147, 151].

Some have found that co-detections found early are not associated with increased morbidity or mortality [152]. Payson et al. [153] determined that very young children with COVID-19 were less likely to suffer from serious bacterial infections compared to a control group with other virus infections. High rates of co-infections nevertheless are generally associated with worse disease and with mortality among other populations [118, 123, 126, 132, 137, 138, 141, 142, 154–158]. Bacterial co-infections have an increased frequency as patient age advances [125, 155]. The greater the presence of patient co-morbidities, the more frequent the finding of co-incident infections [125, 135]. Gram-negative bacillus infections are associated with increased hospital stay and severe COVID-19 [118, 140, 157–160]. They more often arise either in the respiratory tract, with intravenous access devices, or with genitourinary foci [145, 155, 156, 158, 160]. Bacteremias tend to be less common but are more likely to be seen with intensive care patients [77, 145, 156, 159, 161]. A low rate of COVID-19-associated community-acquired bacteremia has been reported despite the high frequency of COVID-19-related deaths [162]. Cusumano et al. [163] particularly find that Staphylococcus aureus bacteremia may be an important predictor of worse outcome. There is an increasing antibiotic resistance profile with co-infection [122, 123, 127, 135, 137, 140, 142, 144, 146, 157, 159, 160, 163, 164]. For example, some American centers have been particularly inundated with multi-resistant coliforms [135, 157]. Hughes et al. [49] found that co-infection rates do not differ substantially when comparing patients with COVID-19 to those with purely influenza virus. The phenomenon of COVID-19 co-infection with bacteria that are existing with or evolving hypervirulent traits is in its infancy for research [148]. Changes to usual hospital infection control in times of complicating patient surge must be considered in the context of increasing nosocomial infection [159]. Imperative in the control of both COVID-19 and associated nosocomial infections is the due regard that must be given to appropriate environmental containment strategies [6, 165].
Conclusion

There is generally a low rate of new bonafide viral co-infections in early COVID-19 as currently appreciated. Reports of high co-infection rates must be tempered by limitations in current diagnostic methods. Inevitably, COVID-19 will occur superimposed on existing infections, and by virtue of the frequency of COVID-19, other superimposed infections will occur during a SARS-CoV-2 infection. In the context of increasingly severe COVID-19, opportunistic and nosocomial infections will occur due to the prolonged and intense nature of some diseases and the common use of both antibiotics and immunomodulatory treatments. Further data accumulation is justified, and further insight into co-infections with COVID-19 will provide better guidance for effective antimicrobial therapy whether for SARS-CoV-2 or bonafide co-infections.

The general precautions used for COVID-19 prevention have clearly reduced the frequency of other concurrent and seasonal viral respiratory infections. As vaccines are implemented and control strategies are proportionately relaxed, the general background prevalence of seasonal respiratory viruses will return at which time it may be anticipated that co-infections with SARS-CoV-2 will increase, and this topic will become of increasing relevance and complexity.

Code Availability Not applicable.

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Data availability Not required.

Declarations

Ethics Approval Ethics approval is not required for this review.

Consent to Participate Consent is not required for the review.

Consent for Publication There is only one author.

Conflict of Interest The author declares no competing interests.

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