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Bacterial co-infections with SARS-CoV-2

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Abstract

The pandemic coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has affected millions of people worldwide. To date, there are no proven effective therapies for this virus. Efforts made to develop antiviral strategies for the treatment of COVID-19 are underway. Respiratory viral infections, such as influenza, predispose patients to co-infections and these lead to increased disease severity and mortality. Numerous types of antibiotics such as azithromycin have been employed for the prevention and treatment of bacterial co-infection and secondary bacterial infections in patients with a viral respiratory infection (e.g., SARS-CoV-2). Although antibiotics do not directly affect SARS-CoV-2, viral respiratory infections often result in bacterial pneumonia. It is possible that some patients die from bacterial co-infection rather than virus itself. To date, a considerable number of bacterial strains have been resistant to various antibiotics such as

azithromycin, and the overuse could render those or other antibiotics even less effective. Therefore, bacterial co-infection and secondary bacterial infection are considered critical risk factors for the severity and mortality rates of COVID-19. Also, the antibiotic-resistant as a result of overusing must be considered. In this review, we will summarize the bacterial co-infection and secondary bacterial infection in some featured respiratory viral infections, especially COVID-19.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first identified in December 2019 in Wuhan, China, and is currently circulating throughout the world.[1] By July 5, 2020, more than 11,125,245 million cases have been diagnosed in 216 countries, and more than 528,204 deaths have been reported.[2] The ongoing COVID-19 pandemic highlights the critical need for rapid development of vaccines and antiviral treatments to reduce the number of hospitalizations and deaths caused by this new dangerous coronavirus.[3] Co-infections and superinfections are common in respiratory viral infections.[4,5] According to the laboratory, clinical, and epidemiological studies, secondary or bacterial co-infections with other viruses can significantly increase the mortality rate in patients infected with viral infections.[6,7] It has previously documented that the mortality rate of viral infections can be influenced by different factors, such as bacterial co-infection.[8–10] For instance, influenza-related bacterial infections contribute to severe illness and mortality during the epidemic and seasonal influenza outbreaks.[11] Some influenza-related bacterial species include *Streptococcus pyogenes*, *Neisseria meningitidis*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*.[11–18] The mechanisms of severe complications caused by influenza-bacterial co-infections mainly include a lack of effective immune response as well as pathogenic synergy.[5] Although multiple microbial agents can cause acute lower respiratory tract infections, in most cases, the disease is caused by viruses and bacteria at the same time.[19] Secondary and bacterial co-infections with pandemics and viral epidemics have irreversible consequences, especially in high-risk groups, including those with immunodeficiency or immunosuppression.[20]

Emerging evidence suggests that the number of patients with COVID-19 diagnosed with bacterial co-infections during hospitalization periods is increasingly raised.[21–23] The source and specific nature of these infections are yet to be fully explored, but there is some evidence suggesting that multidrug-resistant bacteria are among the pathogens that are thought to be responsible for the development of these infections.[21–23] Patients vulnerable to viral lung infections, such as influenza, severe acute respiratory syndrome (SARS), and COVID-19 are the greatest risk to be co-infected with superbugs.[21–25] For example, the 2009 H1N1 influenza pandemic caused approximately 300,000 deaths around the world in which 30–55% of cases die of bacterial pneumonia.[26,27] It is now known that viral infections can weaken the host immunity, paving the way for the development of viral-bacterial co-infection.[28,29] The new coronavirus, COVID-19, is another example of this fact as most of the hospitalized patients with COVID-19 acquired a secondary bacterial infection.[30–32] In some severe form of SARS-CoV-2, patients exhibited increased levels of infection-related biomarkers and inflammatory cytokines, suggesting potential bacterial co-infection as a result of the dysregulated immune system.[33] Besides, the emergence of antibiotic resistance could be an additional burden for the health care system as co-infection with coronavirus and pneumonia stretches health care units beyond their capabilities and resources. Understanding the mechanism underlying the synergy between Covid-19 and bacteria paves the way for the discovery of novel therapeutic agents to prevent the mortality rate in patients co-infected with COVID-19 and bacteria. In the current situation, appropriate and systematic analysis of COVID-19 patients diagnosed with bacterial co-infection should be implemented to choose proper antibiotics to increase the survival of patients and limit the spread of drug-resistant bacteria. The use of rapid diagnostic tools and methods promoting the prescription of effective narrow-spectrum antibiotics should be taken into account. In this review, we will summarize the current data available for bacterial infections in patients with COVID-19.

1.1 | Bacterial co-infection with viral respiratory infections

Viral pneumonia and lower respiratory tract infections are well characterized in adult patients, including those diagnosed with severe forms of viral infection.[34] Most viral lower respiratory tract infections seem to be acquired in the community and considered a leading cause of infection in patients who undergo mechanical ventilation.[34] The most common cases diagnosed with bacterial co-infection with viral infections are seen in those infected with influenza virus.[27] The oldest report of bacterial infections that occurred simultaneously or shortly after influenza is related to the 1918 Influenza pandemic, in which most deaths occurred as a result of co-infection with infectious bacteria.[35] Also, the H1N1 Influenza pandemic in 2009 was complicated by bacterial pneumonia in 4–33% of hospitalized patients.[36–38] Bacterial-viral co-infection is not restricted to influenza and also caused by other respiratory viruses, such as parainfluenza virus, respiratory syncytial virus, adenovirus, rhinovirus, and human metapneumovirus.[34,39,40] Despite the discovery of antibiotics and viral vaccines in 1918–1957, the mortality rate, resulting from secondary bacterial pneumonia remained a major problem. The mortality rate seems to be still growing mostly because of the rapid rate of aging in the human population.[41,42]

Although viruses are commonly responsible for the development of acute upper and lower respiratory infections, in most cases patients may be infected by both bacterial and viral pathogens; however, the clinical manifestations at the early stages of the disease would not be nosologically distinguishable for physicians to differentially diagnose viral from a bacterial infection.[43] Recently, a group of respiratory emerging viruses has been identified, such as human coronavirus (HCoV), NL63, human bocavirus, influenza viruses' type H1N1 and H5N1, SARS, Middle East Respiratory Syndrome-related coronavirus (MERS), and Covid-19.[44–48] In children, atypical bacterial pathogens, such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* include the majority of infectious agents that cause mild, moderate, or even severe forms of acute respiratory infections.[49,50] Bacterial co-infections with respiratory viral pathogens are very common, often through synergistic interaction among viruses such as influenza virus, and bacterial pathogens and the host immune system of the human being; nevertheless, the interaction between viruses and unusual bacteria is not yet fully understood.[50,51] These secondary infections predominantly involve a specific group of bacterial pathogens, such as *S. aureus*, *S. pneumoniae*, *S. pyogenes*, and *H. influenzae*.[11–18] A complete list of bacterial co-infections with viral pathogens is depicted in Table 1.

1.2 | Viral predisposition to bacterial co-infection in the respiratory tract

Commonly, viral infection can destroy histologically and functionally the respiratory tract of individuals upon viral spread.[42] Depending on the type of the virus, the histopathological outcomes could be relatively different from mild types to severe ones. These detrimental changes include altered mucus secretion, cell death, hyperplasia, decreased mucosal clearance, reduced oxygen exchange, and impaired surfactant secretion.[42,77] Each of these effects is caused by various molecular mechanisms, depending on the virus, bacterial species, as well as the degree of the host immune reaction to either a bacterium or virus.[42] It has been noted that viral infections promote bacterial colonization of the airway through a variety of mechanisms.[42] Peltola and colleagues found that influenza viruses can enhance the colonization of the nasopharynx by *S. pneumoniae* bacterium, however, only particular subtypes were found to mediate the development of bacterial otitis media and sinusitis.[78] These data explain why the rate of bacterial infection is high in influenza seasons.[42] The neuraminidase enzyme of the influenza virus has been found to be presented on the host cell receptors, and they are employed for the adherence of bacteria due to its sialidase ability that changes the carbohydrate moieties on the host epithelial cells.[77,79] This enzyme is also capable of increasing the possibility of bacterial adherence to the host cells through the stimulation of transforming growth factor-beta (TGF-β) which triggers the up-regulation of integrins and fibronectin. Integrins and fibronectin have been shown to act as receptors for bacteria.[80] Besides, interferons (IFNs) induction of by influenza virus can cause reduced C-C Motif Chemokine Ligand 2 (CCL2) expression resulting in failed macrophages recruitment that necessary for clearance of pneumococcal cells thereby enhance the colonization of *S. pneumoniae* in vivo.[81] Also, it has been found that the influenza virus predisposes the host to develop pneumonia caused by *S. aureus* where viral and bacterial loads are increased during co-infection.[52] It has been hypothesized that viral load is increased following bacterial co-infection because of increased shedding rate of the virus from infected host cells; however, bacterial loads would be elevated as a result of impaired function of alveolar macrophages.[82]

Additionally, other upper respiratory tract viruses increase the adherence ability of bacterial pathogens to primary and immortalized epithelial cells with particular differences. Such differences are determined by the types of epithelial cells and their response to parainfluenza virus-3, respiratory syncytial virus, and/or influenza virus.[83] Novotny et al[84] showed that adenovirus and respiratory

TABLE 1 Common respiratory viral-bacterial coinfections and their associated clinical infections in human

Viral infection	Bacterial coinfection	Clinical infection	References
Influenza	*Staphylococcus aureus*, MRSA	Community-acquired pneumonia,	18,52–57
	Streptococcus pneumoniae	Pneumococcal pneumonia, sepsis, meningitis, otitis media	58
	Streptococcus pyogenes (group A streptococci)	Sepsis, pleural empyema	15
	Haemophilus influenzae	Pneumonia	59
	Moraxella catarrhalis	Pneumonia and bacteremia	60,61
	Neisseria meningitidis	Meningococcemia	62,63
	Chlamydophila pneumoniae	Pneumonia	64
	Mycoplasma pneumoniae	Pneumonia	64
	Legionella pneumophila, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Burkholderia cepacia, Enterobacter aerogenes	Pneumonia	57
Metapneumovirus	*Haemophilus influenzae*, enterococcus spp, *N. meningitidis* group B, Brucella spp, *Streptococcus pyogenes, Streptococcus pneumoniae*	Acute otitis media, pneumonia	65
Respiratory syncytial virus	*Pseudomonas aeruginosa*	Respiratory infections in cystic fibrosis patients	66,67
Adenovirus	Non-typeable *Haemophilus influenzae, Chlamydia trachomatis*	Pneumonia or acute otitis media	68
Parainfluenza	*Streptococcus pneumonia, Streptococcus agalactiae, Haemophilus influenza*	Acute otitis media, pneumonia	69,70
Rhinovirus	*Streptococcus pneumonia, Mycoplasma*	Pneumonia	50
	Staphylococcus aureus	Respiratory complications	71
SARS	*Chlamydophila pneumonia Mycoplasma pneumonia*	Pneumonia	72
	MRSA	Pneumonia	73,74
MERS	*Mycobacterium tuberculosis*	Immune suppression and augment the infection of each other	75
	Mycoplasma spp. *Legionella Chlamydia* spp.	Not reported	76

Abbreviations: MERS, Middle East respiratory syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; SARS, severe acute respiratory syndrome.

syncytial virus stimulated the expression of intercellular adhesion molecule 1 (ICAM-1) by primary respiratory tract epithelial cells. ICAM1 acts as a receptor for Type 4 pilus (T4P) of non-typeable *H. influenzae* (NTHI), thus promoting the binding of this pathogen to cells expressing this molecule. Also, respiratory syncytial virus infection increases the binding ability of *P. aeruginosa* to normal epithelial cells, as well as cells affected by cystic fibrosis. Such phenomena have been frequently employed by other bacteria to increase their virulence to infect the cells.[66] Studies have indicated that, following the infection with the respiratory syncytial virus, the rate of the binding of *S. pneumoniae* serotypes epithelial cells is increased by 2–10 folds.[85] Similarly, the antibody titers against *S. pneumoniae* are elevated in the nasopharynx when the cells co-infected with the respiratory syncytial virus, rhinovirus, and community-acquired pneumonia.[86] The higher degree of colonization of nasopharynx with *S. pneumoniae*

is also found when the individuals are co-infected with viral upper respiratory tract infection or human immunodeficiency virus infection.[87]

Bacterial and viral co-infection can alter some properties of the host mucosal immunity, leading to the failure in controlling the replication of bacteria in this site.[88,89] Some key findings are discussed here, including the influence of viral infection on phagocytic activity. The reduction of alveolar macrophages by the influenza virus facilitates bacterial co-infection.[88,90] Several lines of evidence demonstrated that 90% of resident alveolar macrophages were lost in the early weeks after influenza infection through tracking dye-labeled alveolar macrophages,[42] whereas 95% of the initial bacterial inoculum was eliminated during 3 hr by alveolar macrophages in non-influenza inoculated hosts. Notably, in those cells co-infected with influenza virus about 50% of the bacterial inoculum remained recoverable.[42] Also, it has been suggested that phagocyte activity, along with the cell proliferation could be influenced by viral infection. The infection of alveolar macrophages with influenza causes a marked decrease in the level of cytokines and chemokines, leading to decreased rates of recruitment and stimulation of neutrophils.[88] It may also suppress the phagocytic bacterial clearance mediated to nicotinamide adenine dinucleotide phosphate (NADPH), thereby increasing the susceptibility to secondary bacterial infection.[91] As mentioned earlier, the dysregulation of proinflammatory cytokine-induced by viral infection has been shown to play an essential role in the susceptibility of the cells to secondary bacterial infection. It is now known that type 1 IFNs have antiviral and immune-stimulatory properties and could have detrimental effects on human cells when their expression is inappropriate and excessive. It has been reported that IFNs play a fundamental role in the production of anti-inflammatory cytokines, such as interleukin (IL)-10 and IL-6, as well as the inhibition of proinflammatory cytokines, linking the innate immunity to adaptive immune responses, such as IL-17 and IL-23. They also decrease the activity of macrophages, dendritic cells, natural killer cells, along with the number of CD4- and CD8-positive T cells, leading to the impaired eradication of bacterial co-infection.[79,92–94]

Also, there are a number of mechanisms that are independent of the phagocytosis process by which viral host infection can predispose the human body to secondary bacterial co-infection. The production of antimicrobial peptides (AMPs), such as lipocalin-2, cathelicidin, Regenerating Islet Derived Protein 3 Beta (REG3B), calprotectin, may be dysregulated by upper respiratory tract viruses.[94] The respiratory syncytial virus infection is able to diminish the expression of human β-defensin-3 orthologue named chinchilla beta-defensin 1 when used in vivo. Of note, con-infection with the respiratory syncytial virus is capable of stimulating the viral load of *Nontypeable Haemophilus influenzae* (*NTHi*) in the nasopharynx by 10–100 folds.[95] The intranasal delivery of anti-chinchilla beta-defensin 1, human β-defensin 3, or the recombinant form of chinchilla beta-defensin 1 showed that the disruption of the availability of even a single innate immune effector could have a great impact on bacterial load since the viral infection has a critical in the loading of *H. influenzae* within the host airway.[95] Some mechanisms by which viral respiratory infections may predispose patients to bacterial infections to include failure immune response, viral-induced changes in epithelial cells, and the increased bacterial colonization[34] and summarize of the potential mechanisms responsible for bacterial coinfection with viral respiratory infections is depicted in Table 2.

1.3 | Coronaviruses influence on host immune system

The human immune reaction to SARS-CoV-2 infection is a two-step reaction that during the non-severe infection phase, a particular adaptive immune reaction is necessary to viral eradicate and prevent the disease from progressing to a severe phase.[127,128] Hence, approaches to increase immune reactions such as using anti-serum and Pegylated IFNα are crucial at this phase.[127,128] To provide a protective immune reaction in the early phase, the host must be in a good general health condition and have a genetic background to be able to exhibit an acceptable antiviral reaction. Genetic diversity is well known to involve in particular changes in the host immune response to various microbial pathogens.

There is few information about the initial events in the process of virus elimination and inflammatory reactions during SARS-CoV infection. However, the innate immune reactions is mediated to the adaptive immunity development and disease severity in SARS-CoV.[129] Of note, SARS-CoV evolved escape mechanisms to avoid IFN responses in infected host cells. Besides, inflammatory reactions are regulated by inflammatory cytokines and chemokines such as IL-6, interferon-γ-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1) as well as the penetration of inflammatory cells such as macrophages into infected host tissues.[129] The suppression of antiviral type I interferons is one of the marked characteristics of SARS-CoV infection as well as other group II coronaviruses including mouse hepatitis virus.[130] It has been shown that the formation of type I interferons is impaired in host cells infected with SARS-CoV, but pretreatment of cells with IFN suppresses the growth of SARS-CoV.[131,132] This shows that these viruses

TABLE 2 Summary of the potential mechanisms responsible for the bacterial coinfection with viral respiratory infections

Mechanism	Description	References
Elevation in bacterial adherence due to viral infection	Virus can modulate surface membrane receptors, thereby enhancing bacterial adhesion	16,96–98
Cell destruction by viral enzymes	Viral enzymes destroy mucosal glycoproteins, mainly those inhibiting bacterial attachment	98,99
Reduction of mucociliary clearance	Virus can reduce mucociliary clearance leading to the decreased production of bactericidal materials	100
Reduction in chemotaxis	Virus can decrease the chemotactic factors, leading to the reduced cell response to attacking organisms	101
Direct effect on phagocytic and induction of post phagocytic alveolar macrophage functions	Virus hinders or modifies a number of immune functions, such as phagosome-lysosome fusion and intracellular killing	102,103
Induction of immature phagocytes	Virus can disrupt macrophages and probably replace them with immature phagocytes	98,104,105
Reduction of surfactant levels	Virus impairs the function of alveolar type-2 pneumocyte	98,106,107
Induction of dysbiosis in lower respiratory tract microbiome	Microbiome dysbiosis can affect the immune response against respiratory viral infection	108
Dysregulation of the innate and adaptive immune responses	Virus decreases the number of alveolar macrophages through the development of apoptosis	42,88,90,91
Modulation of apoptosis and inflammation	Autophagy and apoptosis facilitates secondary bacterial pneumonia after viral infection	109
Reduction of antibacterial immune function at the respiratory epithelium	Respiratory viral infection leads to the predisposition to secondary bacterial infection via the deviation of the respiratory tract immune status	110–115
Dysregulation of nutritional immunity	Some viruses can subvert nutritional protection to promote bacterial infection	116–118
Immunosuppression	Immunosuppression is induced by several viruses such as HIV	119–121
Synergism during viral/bacterial co-infections	Both viruses and bacteria play a role in the immunopathogenicity of co-infection	8,122,123
Release of planktonic bacteria from biofilms	Viruses can manipulate many factors such as chemokines and hydrogen peroxide, thereby leading to the disruption of biofilm structure	42,124–126

Abbreviation: HIV, human immunodeficiency viruses.

have developed mechanisms to overcome IFN responses in infected cells. Type I interferons are rarely found in acute SARS patients, and SARS-CoV is sensitive to Pegylated IFN-α, as shown in in vivo murine models.[133] Studies indicated that type I interferon suppression in SARS-CoV-infected hosts is mediated by the inactivation

of the IRF-3 (interferon regulatory factor 3) protein, a transcriptional factor that controls the transcription of interferons.[132] Also, other SARS-CoV accessory proteins act as powerful interferon antagonists through various strategies.[129] For instance, N proteins inhibit the expression of interferons, whereas open-reading frame 3b and 6 proteins oppress the signaling pathway and expression of interferons.[129] Also, open-reading frame 6 proteins can halt the translocation of signal transducer and activator of transcription 1 (STAT1). The open-reading frame 3b protein is a shuttling protein, impeding the stimulation of type I interferon, which is triggered by retinoic acid-inducible gene 1 (RIG-I) and mitochondrial antiviral-signaling (MAVS) protein.[134] Additionally, M proteins suppress the production of type I interferon by inhibiting the generation of the TNF Receptor Associated Factor 3 (TRAF3)–TRAF Family Member Associated NFKB Activator (TANK) – TANK binding kinase 1 (TBK1)/IκB kinase ε (IKKε) complex.[134] Besides, SARS-CoV NSP1 proteins are able to halt the expression of IFN-β in host cells by promoting the degradation of the host mRNA and the suppression of the translation process.[135] A polyprotein complex of SARS-CoV named papain-like protease is able to inhibit the phosphorylation and nuclear translocation of IRF-3, resulting in disrupting the activation of type I IFN response via either Toll-like receptor 3 (TLR-3) or RIG-1/melanoma differentiation-associated gene 5 (MDA5) complex.[136] Also, infected cells with SARS-CoV can stimulate the expression of protein kinase R (PKR) and PKR-like endoplasmic reticulum kinase (PERK).[137]

1.4 | Bacterial co-infection with coronaviruses and COVID-19

Although numerous studies performed on viral and bacterial co-infections, little information exists about human coronaviruses. In addition to seasonal influenza, it has been reported corona pathogens of pneumonia include coronavirus 229E, NL63, OC43, SARS, MERS, and SARS-CoV-2. These viruses can cause co-infection in the setting of community-acquired bacterial pneumonia.[138–141] Human coronavirus NL63 (HCoV-NL63) has been recently discovered as a human respiratory pathogen with a high worldwide prevalence.[142,143] Arguably, HCoV-NL63 is among the most clinically significant human coronaviruses and associated with upper and lower respiratory tract infections, frequently occurring in the winter and presenting more severe symptoms in children, the elderly, and immunocompromised patients.[142–144] In a study conducted by Golda et al.,[143] they evaluated the impact of HCoV-NL63 on bacterial adherence causing respiratory tract diseases. HCoV-NL63

infection has been shown to enhance the adherence of *S. pneumoniae* to cells infected with the virus.[143] In one study, Zahariadis et al.[72] showed the coinfection of SARS patients with other pulmonary pathogens. They found that 30 and 9% of cases with SARS were co-infected with *C. pneumoniae* or *M. pneumonia*, respectively. Additionally, Alfaraj et al.[75] reported the coinfection of MERS-CoV with tuberculosis (TB) in two cases. In a study carried out by Wang et al.,[145] they reported seven cases of SARS-related deaths who developed a secondary bacterial infection.

The COVID-19 pandemic caused a large number of immunocompromised individuals to be hospitalized and some reports indicated that some COVID-19 patients were diagnosed with secondary infections.[30–32] The specific source and nature of these infections have not yet been fully investigated; however, there is evidence indicating that multidrug-resistant bacteria are among those microbes responsible for the development of these secondary infections. In one study, five cases (5.1%) with bacterial co-infections including *Acinetobacter baumannii* and *Klebsiella pneumoniae* were found among 99 patients,[146] while in another study, four cases (9.8%) with secondary bacterial infections were reported among 41 patients.[147] In a study performed by Zhang et al.,[148] 221 patients with SARS-CoV-2 pneumonia were admitted to Zhongnan Hospital, Wuhan, China. Among them, 25.8% (57/221) patients were afflicted with co-infections, and among these patients with co-infections, 29.8% (17/57) were co-infected with bacteria. In a study conducted by Blasco et al.,[149] they detected one patient who was positive for *M. pneumoniae* coinfection among patients with COVID-19 pneumonia. Also, Claire et al.[150] reported a fatal case of necrotizing pneumonia induced by Panton-Valentine leukocidin–secreting *S. aureus* in a patient who was affected by COVID-19.

Some patients infected with SARS-CoV-2 showed the increased levels of biomarkers and inflammatory cytokines related to co-infection by bacteria, caused by dysregulation in the immune system.[33] The management of the severe form of SARS-CoV-2 is similar to most viral pneumonia-causing respiratory failure. In a study carried out by Bordi et al.,[151] they detected *M. pneumoniae* in five patients (4.0%), while only one patient was infected with *L. pneumophila* and *S. pneumoniae* (0.8%), and mixed infections were also observed in a small number of cases. They found the importance of using a broad-spectrum molecular diagnostic panel for rapid detection of the most common respiratory pathogens to improve evaluation and clinical management of patients with a respiratory syndrome consistent with COVID-19.[151] A list of bacterial co-infection with COVID-19 is depicted in Table 3.

One reason for this bacterial co-infection is due to many hospital-associated bacteria being adapted to develop

TABLE 3 List of bacterial co-infection with COVID-19

Bacterium	Infection	References
Staphylococcus aureus	Necrotizing pneumonia	152
Mycoplasma pneumoniae	Exacerbate clinical symptoms, increase morbidity and prolonged intensive care unit stay	153
Legionella pneumophila	Pneumonia	154
Enterobacter cloacae	Pneumonia	155
Acinetobacter baumannii	Pneumonia	146,155
Klebsiella pneumoniae	Pneumonia	146
Mycoplasma pneumoniae	Interstitial pneumonia	149
Mycoplasma pneumoniae	Not reported	151
Legionella pneumophila	Not reported	151
Streptococcus pneumoniae	Not reported	151
Prevotella	Not reported	156–158
Haemophilus	Not reported	158,159
Lautropia	Not reported	159
Cutibacterium	Not reported	159

an infection in individuals with a weakened immune system. It has been noted that the SARS-CoV-2 infection can damage the cells and the lung infrastructure.[160] Subsequently, the changed condition enables bacteria to increase adherence and invasion (Figure 1). It has been found that the mortality rate of viral pandemics is heavily impacted by secondary bacterial infections with myriad numbers of people in the 1918 influenza pandemic as well as the 2009 pandemic, who died from secondary bacterial infections rather than the virus alone.[26,27,161]

Despite the proven significance of co-infections in the severity of respiratory diseases, these kinds of infections during large outbreaks of respiratory infections are underdetermined.[162] For the precise diagnosis and evaluation of co-infections during the COVID-19 pandemic, samples must be taken longitudinally throughout the disease course via techniques independent of the culture for identifying mixed infections such as whole-genome metagenomics (WGMs).[162] Such works offer valuable monitoring findings on co-infection pathogens and drug-resistance infections resulting in improved antibiotic prescribing options.[162]

Zhou et al.[163] found that in the current COVID-19 pandemic, 50% of patients who died from Covid-19 had bacterial co-infections. Correspondingly, Chen et al.[146] have reported fungal and bacterial co-infections in patients with COVID-19. COVID-19 patients are hospitalized on invasive mechanical ventilation for a long time, leading to higher chances of using a ventilator and hospital-acquired infections.[162] Thus, the rapid diagnosis of a broad range of potential pathogens and antimicrobial resistances for subsequent monitoring of co-infection would be crucial. The metagenome of COVID-19 patients has shown that Prevotella is a key player in immune response in a Chinese study,[156] while other opportunistic pathogens were found in a study conducted in the USA.[157–159,164] There is a wide range of bacterial pathogens including Haemophilus, Lautropia, Prevotella have been detected as co-infection in Brazil, China, and the USA.[157–159,164]

However, a further concern with the rapid expansion of critical care capacity to manage SARS-CoV-2 can potentially increase the rate of nosocomial infection within the hospital environment.[165] To date, although the role of viral or bacterial co-infection in SARS-CoV-2 remains elusive, only a few SARS-CoV-2 patients worldwide have had documented evidence of co-infection; however, there is still a concern on this issue as many reports claim that a significant proportion of COVID-19 patients developed bacterial co-infections.

1.5 | The era of post-COVID-19 and antimicrobial resistance bacteria

It has been noted during the current pandemic, the antibiotic administration has been frequently used for COVID-19 patients who were admitted to the intensive care unit.[165] While scientists attempt to understand and control the COVID-19 pandemic, it would be also critical to prepare for the effect of the current and future viral pandemics on secondary bacterial infections, resulting in antimicrobial resistance in the near future. In combination with using an antimalarial drug, hydroxyl-chloroquine, azithromycin has become a popular therapeutic option for COVID-19 patients. Reports demonstrated that a combination of hydroxyl-chloroquine and azithromycin was effective for a large proportion of Covid-19 patients.[166,167] It is hard to estimate how often this combination is prescribed, but such a rate would be high enough to cause a shortage of azithromycin. However, 30–40% of common types of bacterial agents are already resistant to azithromycin, and overuse could render this or other antibiotics even less effective.[168] The findings could help experts' advice on using the antibiotics in COVID-19 patients and help them to better understand the spread of
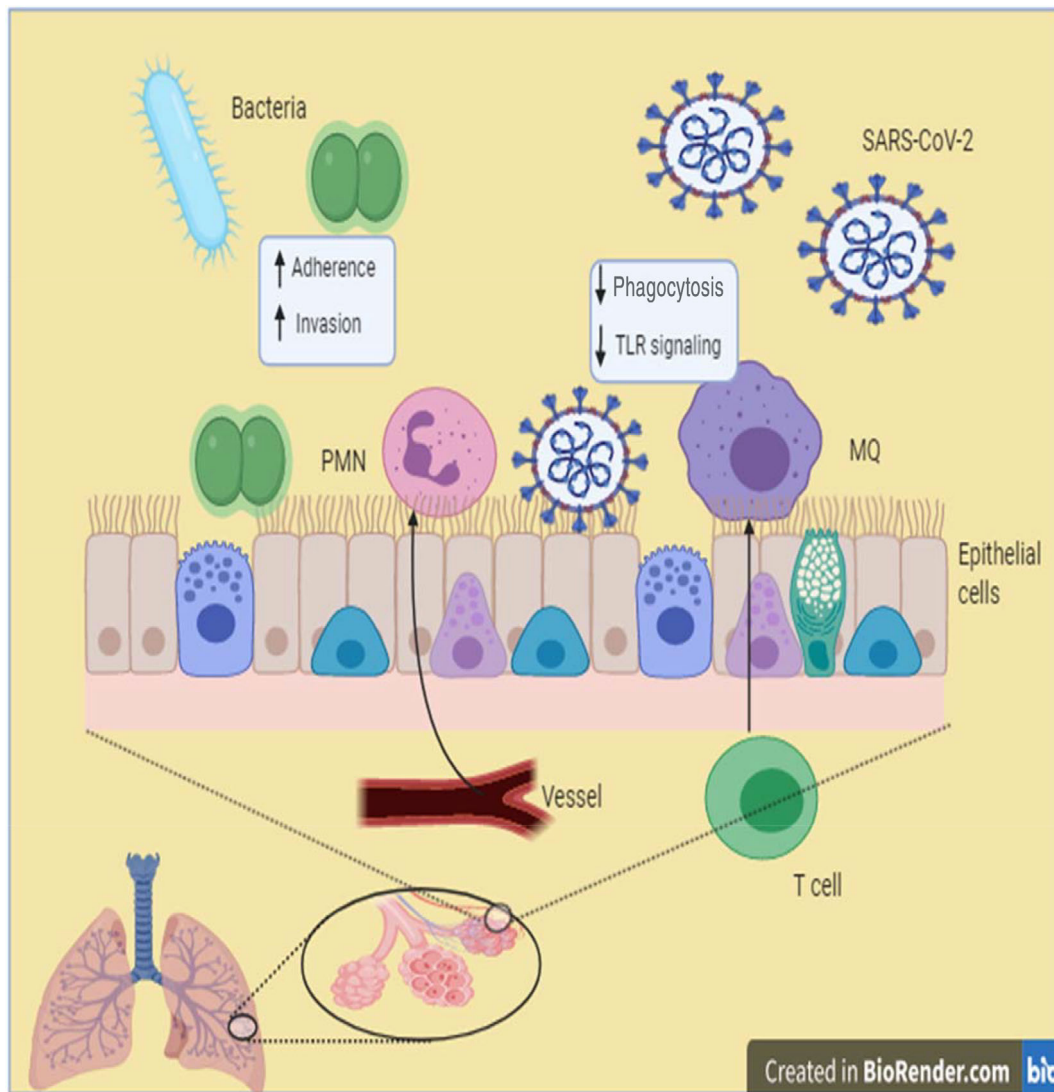
FIGURE 1   Postulated schematic of bacterial coinfection with SARS-CoV-2 infection. It has been proposed when SARS- CoV-2 infects lung cells can damage the cells and the lung infrastructure.[160] This situation attracts neutrophil and macrophages to the site of infection and promoting the inflammation.[160] Finally, the changed situation and epithelial damage can cause bacteria to adhere to and invasion of the cells and proliferation. MQ, macrophage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

co-infections in hospitals and the mechanism of bacterial-viral coinfection. One factor that involves in the antibiotic resistance in bacterial co-infection is the widespread use of antibiotics in COVID-19 patients. Emerging data show that more than 90% of COVID-19 patients receive antibacterial drugs.[169,170] This rapid increase in antibiotic administration can cause a strong selective pressure on bacterial pathogens to evolve resistance leading to the increased incidence of drug-resistant bacterial infections in the years subsequent to the COVID-19 pandemic. It was estimated that 10 million people could die from an antibiotic-resistant bacterial infection in the year of 2050,[171] but such prediction may be altered and shortened because of the devastating impact of the COVID-19 pandemic on the usage of antibiotics, so this timeline

will almost have to be modified. Nevertheless, concerted efforts must be made to better understand antibiotic administration in COVID-19 patients. Antibiotics do not directly act on viral infections but viral respiratory infections often lead to bacterial co-infections.[30–32] The current pandemic highlights the necessity for understanding the complex relationship between viral and bacterial infections. Of note, in patients who have treated with high-dose antibiotics may have more co-infections with drug-resistant bacteria.

Additionally, a recent clinical trial conducted by Hagan et al[172] demonstrated that the use of broad-spectrum antibiotics (which led to depleting gut microbiota) decreased and impaired the immune system's ability to generate antibodies. Also, the current study shows that the use of

TABLE 4 Several functional suggestions for management and control of bacterial co-infection with COVID-19

Suggestion	Description
Using a broad-spectrum diagnostic panel	Improves diagnosis, evaluation, and clinical management of patients with other respiratory viral infection concurrent with COVID-19
Developing novel treatment and prevention strategies	Increases our knowledge about the underlying molecular mechanisms accounting for viral-bacterial co-infection to promote novel therapeutic and prevention approaches
Performing antibacterial susceptibility tests and potential therapy	Prevents reduced antimicrobial susceptibility and treatment failure due to co-infections[174]
Considering the biofilm-associated bacterial infections	Facilitates treatment management as biofilm formation on artificial devices has been observed previously, thereby affecting infection outcomes, especially in COVID-19 patients under mechanical ventilation[175]
Classifying mechanisms of pathogen interactions	Increases the ability of infection control as the extension of chemotherapy-resistant pathogens is a severe global obstacle[174]

antibiotics perturbed bile acid metabolism and induced inflammatory responses.[173] Hence, improved functional therapies, including antibiotics and alternative therapies as well as the prediction of bacterial respiratory infections using vaccines, should be regarded as potential therapeutic approaches. Besides, standard guidelines should also be established for the administration of the antibiotics. In addition to the direct effect on drug-resistant bacteria as a result of enhanced antibiotic administration, the transmission of drug-resistant bacteria through the medical system should be taken into account. The COVID-19 pandemic has highlighted the importance of vaccination, the need for functional antimicrobials, as well as the necessity for supporting research into the understanding and control of co-infections. Rapid characterization of co-infection is essential in the treatment of the most COVID-19 patients, and could help to save lives, and will improve antimicrobial stewardship during the pandemic. Additionally, mixed bacterial-viral infections can result in antibiotic treatment failure. These observations show that a better understanding of the underlying mechanisms will enable researchers to design effective preventive and therapeutic options. Several functional suggestions for management and control of bacterial co-infection with COVID-19 are offered in Table 4.

2 | CONCLUSION

Respiratory viruses such as SARS-CoV-2 are well-characterized to cause severe disorders and pneumonia, particularly in individuals with serious medical comorbidities and aged populations. Additionally, respiratory virus infection could usually lead to enhanced susceptibility to secondary bacterial infections. However, the mechanisms responsible for bacterial-SARS-CoV-2 co-infection require further study. It has been noted that an elicited adaptive immune reaction toward viral infection fails the reaction of the host innate immunity against bacterial infection. This situation can explain why bacterial co-infections occur when the virus starts to be eradicated from the lungs of patients with COVID-19. This is accompanied by a shift in phagocytic activity of lung cells that mediate basal levels of innate protection via phagocytosis and pro-inflammatory cytokines formation to cells better attuned to antigen presentation and stimulation of adaptive immune reactions. Additionally, recently it has been found the microbiome diversity shapes our immune system. In line with this, the depletion of the gut microbiome hinders the immune system's ability to create a humoral response against viruses like the flu virus. However, this novel paradigm ultimately allows the development of new immune intervention approaches for the prevention and management of viral-bacterial co-infections in COVID-19 patients. The COVID-19 pandemic reinforces the importance of preventative measures such as vaccination and antimicrobial treatments in maintaining human health.

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REFERENCES
1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395:470–473.
2. Organization T.W.H. Coronavirus disease (COVID-19) pandemic. 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019.

3. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J. 2020;39:355.

4. McArdle AJ, Turkova A, Cunnington AJ. When do co-infections matter? Curr Opin Infect Dis. 2018;31:209.

5. Paget C, Trottein F. Mechanisms of bacterial superinfection post-influenza: A role for unconventional T cells. Front Immunol. 2019;10:336–336.

6. Beadling C, Slifka MK. How do viral infections predispose patients to bacterial infections? Curr Opin Infect Dis. 2004;17: 185–191.

7. Metzger DW, Sun K. Immune dysfunction and bacterial coinfections following influenza. J Immunol (Baltimore, MD: 1950). 2013;191:2047–2052.

8. Jia L, Xie J, Zhao J, et al. Mechanisms of severe mortality-associated bacterial co-infections following influenza virus infection. Front Cell Infect Microbiol. 2017;7:338.

9. Katsurada N, Suzuki M, Aoshima M, Yaegashi M, Ishifuji T, et al. The impact of virus infections on pneumonia mortality is complex in adults: A prospective multicentre observational study. BMC Infect Dis. 2017;17:755.

10. Quah J, Jiang B, Tan PC, Siau C, Tan TY. Impact of microbial Aetiology on mortality in severe community-acquired pneumonia. BMC Infect Dis. 2018;18:451.

11. Smith AM, McCullers JA. Secondary bacterial infections in influenza virus infection pathogenesis. Curr Top Microbiol Immunol. 2014;385:327–356.

12. Abbasi S, Pendergrass LB, Leggiadro RJ. Influenza complicated by *Moraxella catarrhalis* bacteremia. Pediatr Infect Dis J. 1994;13:937–938.

13. Jacobs JH, Viboud C, Tchetgen ET, Schwartz J, Steiner C, et al. The association of meningococcal disease with influenza in the United States, 1989-2009. PloS One. 2014;9: e107486-e107486.

14. Mulcahy ME, McLoughlin RM. *Staphylococcus aureus* and influenza A virus: Partners in coinfection. mBio. 2016;7: e02068–e02016.

15. Ochi F, Tauchi H, Jogamoto T, et al. Sepsis and pleural empyema caused by *Streptococcus pyogenes* after influenza a virus infection. Case Rep Pediatr. 2018;2018:4509847.

16. Rowe HM, Meliopoulos VA, Iverson A, et al. Direct interactions with influenza promote bacterial adherence during respiratory infections. Nat Microbiol. 2019;4:1328–1336.

17. Su I-C, Lee K-L, Liu H-Y, Chuang H-C, Chen L-Y, Lee YJ. Severe community-acquired pneumonia due to *Pseudomonas aeruginosa* coinfection in an influenza a (H1N1) pdm09 patient. J Microbiol Immunol Infect. 2019;52:365–366.

18. Sun K, Metzger DW. Influenza and *Staphylococcus aureus* coinfection: TLR9 at play. Trends Microbiol. 2019;27: 383–384.

19. Dasaraju PV, Liu C. Chapter 93: Infections of the respiratory system. Medical microbiology. 4th ed. Galveston: University of Texas Medical Branch at Galveston, 1996.

20. MacIntyre CR, Bui CM. Pandemics, public health emergencies and antimicrobial resistance - putting the threat in an epidemiologic and risk analysis context. Arch Public Health. 2017;75:54–54.

21. Bengoechea JA, Bamford CG. SARS-CoV-2, bacterial co-infections, and AMR: The deadly trio in COVID-19? EMBO Mol Med. 2020;12(7):e12560.

22. Hendaus MA, Jomha FA. Covid-19 induced superimposed bacterial infection. J Biomol Struct Dyn. 2020;1–10.

23. Rawson TM, Moore LS, Zhu N, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020.

24. Cauley LS, Vella AT. Why is coinfection with influenza virus and bacteria so difficult to control. Discov Med. 2015;19: 33–40.

25. Sun K, Yajjala VK. Nox2-derived oxidative stress results in inefficacy of antibiotics against post-influenza *S. aureus* pneumonia. J Exp Med. 2016;213:1851–1864.

26. A tool for the potential fall 2009 wave of pandemic H1N1 to guide public health decision-making: An overview of the Public Health Agency of Canada's planning considerations, September 2009. Can Commun Dis Rep. 2010; 36:1–20.

27. Morris DE, Cleary DW, Clarke SC. Secondary bacterial infections associated with influenza pandemics. Front Microbiol. 2017;8:1041.

28. Smith H, Sweet C. Cooperation between viral and bacterial pathogens in causing human respiratory disease. Polymicrobial Diseases. ASM Press, 2002.

29. Almand EA, Moore MD, Jaykus L-A. Virus-bacteria interactions: An emerging topic in human infection. Viruses. 2017; 9:58.

30. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus disease 2019 (COVID-19) and pregnancy: What obstetricians need to know. Am J Obstet Gynecol. 2020;222(5):415–426.

31. Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: A double-edged sword? Lancet. 2020;395:1111.

32. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? Microbes Infect. 2020;22:72–73.

33. Zhang B, Liu S, Tan T, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest. 2020;158(1):e9–e13.

34. Crotty MP, Meyers S, Hampton N, et al. Epidemiology, co-infections, and outcomes of viral pneumonia in adults: An observational cohort study. Medicine (Baltimore). 2015;94: e2332–e2332.

35. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: Implications for pandemic influenza preparedness. J Infect Dis. 2008;198:962–970.

36. Investigators AI. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009;361: 1925–1934.

37. Cillóniz C, Ewig S, Menéndez R, et al. Bacterial co-infection with H1N1 infection in patients admitted with community acquired pneumonia. J Infect. 2012;65:223–230.

38. Rice TW, Rubinson L, Uyeki TM, et al. Critical illness from 2009 pandemic influenza a (H1N1) virus and bacterial co-infection in the United States. Crit Care Med. 2012;40:1487.

39. McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and *Streptococcus pneumoniae*. J Infect Dis. 2003;187:1000–1009.

40. Peltola VT, Murti KG, McCullers JA. Influenza virus neuraminidase contributes to secondary bacterial pneumonia. J Infect Dis. 2005;192:249–257.

41. Rothberg MB, Haessler SD, Brown RB. Complications of viral influenza. Am J Med. 2008;121:258–264.

42. Bakaletz LO. Viral-bacterial co-infections in the respiratory tract. Curr Opin Microbiol. 2017;35:30–35.

43. Korppi M, Don M, Valent F, Canciani M. The value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children. Acta Paediatr. 2008; 97:943–947.

44. Allander T, Tammi MT, Eriksson M, et al. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci. 2005;102:12891–12896.

45. Gatherer D. The 2009 H1N1 influenza outbreak in its historical context. J Clin Virol. 2009;45:174–178.

46. van der Hoek L, Ihorst G, Sure K, et al. Burden of disease due to human coronavirus NL63 infections and periodicity of infection. J Clin Virol. 2010;48:104–108.

47. Abdel-Moneim AS. Middle East respiratory syndrome coronavirus (MERS-CoV): Evidence and speculations. Arch Virol. 2014;159:1575–1584.

48. El ZME, Järhult JD. From SARS to COVID-19: A previously unknown SARS-CoV-2 virus of pandemic potential infecting humans–call for a one health approach. One Health. 2020;9: 100124.

49. Basarab M, Macrae MB, Curtis CM. Atypical pneumonia. Curr Opin Pulm Med. 2014;20:247–251.

50. Baroudy NRE, Refay ASE, Hamid TAA, et al. Respiratory viruses and atypical bacteria co-infection in children with acute respiratory infection. Open Access Maced J Med Sci. 2018;6:1588–1593.

51. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev. 2006;19:571–582.

52. Iverson AR, Boyd KL, McAuley JL, Plano LR, Hart ME, McCullers JA. Influenza virus primes mice for pneumonia from *Staphylococcus aureus*. J Infect Dis. 2011;203:880–888.

53. Robertson L, Caley J, Moore J. Importance of *Staphylococcus aureus* in pneumonia in the 1957, epidemic of influenza a. Lancet. 1958;272:233–236.

54. Severe methicillin-resistant *Staphylococcus aureus* community-acquired pneumonia associated with influenza–Louisiana and Georgia, December 2006–January 2007. MMWR Morb Mortal Wkly Rep. 2007;56:325–329.

55. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: Increase of *Staphylococcus aureus* coinfection. Pediatrics. 2008;122:805–811.

56. Reed C, Kallen AJ, Patton M, et al. Infection with community-onset *Staphylococcus aureus* and influenza virus in hospitalized children. Pediatr Infect Dis J. 2009;28:572–576.

57. Gao H-N, Lu H-Z, Cao B, et al. Clinical findings in 111 cases of influenza a (H7N9) virus infection. N Engl J Med. 2013; 368:2277–2285.

58. Palacios G, Hornig M, Cisterna D, et al. *Streptococcus pneumoniae* coinfection is correlated with the severity of H1N1 pandemic influenza. PloS One. 2009;4:e8540–e8540.

59. Wang X-Y, Kilgore PE, Lim KA, Wang S-M, Lee J, et al. Influenza and bacterial pathogen coinfections in the 20th century. Interdisc Perspect Infect Dis. 2011;2011:146376.

60. Doern GV, Jones RN, Pfaller MA, Kugler K, Group S.P. *Haemophilus influenzae* and *Moraxella catarrhalis* from patients with community-acquired respiratory tract infections: Antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program (United States and Canada, 1997). Antimicrob Agents Chemother. 1999;43:385–389.

61. Simmons WP. *Moraxella catarrhalis* pneumonia and bacteremia in an otherwise healthy child. Clin Pediatr. 1999;38: 560–561.

62. Young LS, LaForce FM, Head JJ, Feeley JC, Bennett JV. A simultaneous outbreak of meningococcal and influenza infections. N Engl J Med. 1972;287:5–9.

63. Jansen AGSC, Sanders EAM, Van Der Ende A, et al. Invasive pneumococcal and meningococcal disease: Association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect. 2008;136:1448–1454.

64. Mina M, Burke R, Klugman K. Estimating the prevalence of coinfection with influenza virus and the atypical bacteria *Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*. Eur J Clin Microbiol Infect Dis. 2014;33: 1585–1589.

65. Wolf DG, Greenberg D, Shemer-Avni Y, Givon-Lavi N, Bar-Ziv J, Dagan R. Association of human metapneumovirus with radiologically diagnosed community-acquired alveolar pneumonia in young children. J Pediatr. 2010;156:115–120.

66. Van Ewijk BE, Wolfs TF, Aerts PC, et al. RSV mediates *Pseudomonas aeruginosa* binding to cystic fibrosis and normal epithelial cells. Pediatr Res. 2007;61:398–403.

67. Petersen NT, Høiby N, Mordhorst CH, Lind K, Flensborg EW, BRUUN B. Respiratory infections in cystic fibrosis patients caused by virus, chlamydia and mycoplasma–possible synergism with *Pseudomonas aeruginosa*. Acta Paediatr. 1981;70:623–628.

68. Korppi M, Leinonen M, Mäkelä PH, Launiala K. Mixed infection is common in children with respiratory adenovirus infection. Acta Paediatr. 1991;80:413–417.

69. Korppi M, Leinonen M, Mäkelä PH, Launiala K. Bacterial involvement in parainfluenza virus infection in children. Scand J Infect Dis. 1990;22:307–312.

70. Tong J, Fu Y, Meng F, et al. The sialic acid binding activity of human parainfluenza virus 3 and mumps virus glycoproteins enhances the adherence of group B streptococci to HEp-2 cells. Front Cell Infect Microbiol. 2018;8:280.

71. Katiyar R, Agarwal V, Chowdhary S, et al. Incidence of human rhinovirus coinfection with *Staphylococcus aureus* among HIV patients suffering from flu like illness. Int J Pharm Sci Res. 2017;8:4441–4446.

72. Zahariadis G, Gooley TA, Ryall P, et al. Risk of ruling out severe acute respiratory syndrome by ruling in another diagnosis: Variable incidence of atypical bacteria coinfection based on diagnostic assays. Can Respir J. 2006;13:17–22.

73. Yap FH, Gomersall CD, Fung KS, et al. Increase in methicillin-resistant *Staphylococcus aureus* acquisition rate and change in pathogen pattern associated with an outbreak of severe acute respiratory syndrome. Clin Infect Dis. 2004;39:511–516.

74. Bassetti S, Bischoff WE, Sherertz RJ. Outbreak of methicillin-resistant *Staphylococcus aureus* infection associated with an

outbreak of severe acute respiratory syndrome. Clin Infect Dis. 2005;40:633–634.

75. Alfaraj SH, Al-Tawfiq JA, Altuwaijri TA, Memish ZA. Middle East respiratory syndrome coronavirus and pulmonary tuberculosis coinfection: Implications for infection control. Intervirology. 2017;60:53–55.

76. Arabi YM, Deeb AM, Al-Hameed F, et al. Macrolides in critically ill patients with Middle East respiratory syndrome. Int J Infect Dis. 2019;81:184–190.

77. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol. 2014;12:252–262.

78. Peltola VT, Boyd KL, McAuley JL, Rehg JE, McCullers JA. Bacterial sinusitis and otitis media following influenza virus infection in ferrets. Infect Immun. 2006;74:2562–2567.

79. Ballinger MN, Standiford TJ. Postinfluenza bacterial pneumonia: Host defenses gone awry. J Interferon Cytokine Res. 2010;30:643–652.

80. Li N, Ren A, Wang X, et al. Influenza viral neuraminidase primes bacterial coinfection through TGF-β–mediated expression of host cell receptors. Proc Natl Acad Sci. 2015;112:238–243.

81. Nakamura S, Davis KM, Weiser JN. Synergistic stimulation of type I interferons during influenza virus coinfection promotes Streptococcus pneumoniae colonization in mice. J Clin Invest. 2011;121:3657–3665.

82. Smith AM, Adler FR, Ribeiro RM, et al. Kinetics of coinfection with influenza a virus and Streptococcus pneumoniae. PLoS Pathog. 2013;9:e1003238.

83. Avadhanula V, Rodriguez CA, DeVincenzo JP, et al. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species-and cell type-dependent manner. J Virol. 2006;80:1629–1636.

84. Novotny LA, Bakaletz LO. Intercellular adhesion molecule 1 serves as a primary cognate receptor for the type IV pilus of nontypeable Haemophilus influenzae. Cell Microbiol. 2016;18:1043–1055.

85. Hament J-M, Aerts PC, Fleer A, et al. Enhanced adherence of Streptococcus pneumoniae to human epithelial cells infected with respiratory syncytial virus. Pediatr Res. 2004;55:972–978.

86. Esposito S, Zampiero A, Terranova L, et al. Pneumococcal bacterial load colonization as a marker of mixed infection in children with alveolar community-acquired pneumonia and respiratory syncytial virus or rhinovirus infection. Pediatr Infect Dis J. 2013;32:1199–1204.

87. Wolter N, Tempia S, Cohen C, et al. High nasopharyngeal pneumococcal density, increased by viral coinfection, is associated with invasive pneumococcal pneumonia. J Infect Dis. 2014;210:1649–1657.

88. Braciale TJ, Sun J, Kim TS. Regulating the adaptive immune response to respiratory virus infection. Nat Rev Immunol. 2012;12:295–305.

89. Lijek RS, Weiser JN. Co-infection subverts mucosal immunity in the upper respiratory tract. Curr Opin Immunol. 2012;24:417–423.

90. Ghoneim HE, Thomas PG, McCullers JA. Depletion of alveolar macrophages during influenza infection facilitates bacterial superinfections. J Immunol. 2013;191:1250–1259.

91. Sun K, Metzger DW. Influenza infection suppresses NADPH oxidase–dependent phagocytic bacterial clearance and enhances

susceptibility to secondary methicillin-resistant Staphylococcus aureus infection. J Immunol. 2014;192:3301–3307.

92. Davidson S, Maini MK, Wack A. Disease-promoting effects of type I interferons in viral, bacterial, and coinfections. J Interferon Cytokine Res. 2015;35:252–264.

93. Mehta D, Petes C, Gee K, Basta S. The role of virus infection in deregulating the cytokine response to secondary bacterial infection. J Interferon Cytokine Res. 2015;35:925–934.

94. Robinson KM, Kolls JK, Alcorn JF. The immunology of influenza virus-associated bacterial pneumonia. Curr Opin Immunol. 2015;34:59–67.

95. McGillivary G, Mason KM, Jurcisek JA, Peeples ME, Bakaletz LO. Respiratory syncytial virus-induced dysregulation of expression of a mucosal β-defensin augments colonization of the upper airway by non-typeable Haemophilus influenzae. Cell Microbiol. 2009;11:1399–1408.

96. Sanford BA, Shelokov A, Ramsay MA. Bacterial adherence to virus-infected cells: A cell culture model of bacterial superinfection. J Infect Dis. 1978;137:176–181.

97. Ramphal R, Small P, Shands J, Fischlschweiger W, Small P. Adherence of Pseudomonas aeruginosa to tracheal cells injured by influenza infection or by endotracheal intubation. Infect Immun. 1980;27:614–619.

98. Galina L. Possible mechanisms of viral-bacterial interaction in swine. Swine Health Prod. 1995;3:9–14.

99. Babiuk LA, Lawman M, Ohmann HB. Viral-bacterial synergistic interaction in respiratory disease. Advances in virus research. Volume 35. Elsevier, 1988; p. 219–249.

100. Iglesias G, Pijoan C. Effect of swine fever live vaccine on the mucociliary apparatus of swine, and its interaction with Pasteurella multocida. Rev Lat Microbiol. 1980;22:52.

101. Kleinerman ES, Daniels C, Polisson R, Snyderman R. Effect of virus infection on the inflammatory response. Depression of macrophage accumulation in influenza-infected mice. Am J Pathol. 1976;85:373.

102. Warr G, Jakab G, Hearst J. Alterations in lung macrophage immune receptor (s) activity associated with viral pneumonia. RES J Reticuloendothel Soc. 1979;26:357–366.

103. Warr GA, Jakab GJ. Alterations in lung macrophage antimicrobial activity associated with viral pneumonia. Infect Immun. 1979;26:492–497.

104. Taneja R, Sharma A, Hallett M, Findlay G, Morris M. Immature circulating neutrophils in sepsis have impaired phagocytosis and calcium signaling. Shock (Augusta, GA). 2008;30:618–622.

105. Grudzinska FS, Brodlie M, Scholefield BR, et al. Neutrophils in community-acquired pneumonia: Parallels in dysfunction at the extremes of age. Thorax. 2020;75:164–171.

106. Ciencewicki J, Gowdy K, Krantz QT, et al. Diesel exhaust enhanced susceptibility to influenza infection is associated with decreased surfactant protein expression. Inhal Toxicol. 2007;19:1121–1133.

107. Kongchanagul A, Suptawiwat O, Boonarkart C, et al. Decreased expression of surfactant protein D mRNA in human lungs in fatal cases of H5N1 avian influenza. J Med Virol. 2011;83:1410–1417.

108. Hanada S, Pirzadeh M, Carver KY, Deng JC. Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia. Front Immunol. 2018;9:2640.

109. Qin Z, Yang Y, Wang H, et al. Role of autophagy and apoptosis in the Postinfluenza bacterial pneumonia. Biomed Res Int. 2016;2016:3801026.

110. Sadler AJ, Williams BR. Interferon-inducible antiviral effectors. Nat Rev Immunol. 2008;8:559–568.

111. Shahangian A, Chow EK, Tian X, et al. Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. J Clin Invest. 2009;119:1910–1920.

112. Robinson KM, McHugh KJ, Mandalapu S, et al. Influenza a virus exacerbates *Staphylococcus aureus* pneumonia in mice by attenuating antimicrobial peptide production. J Infect Dis. 2014;209:865–875.

113. Lee B, Robinson KM, McHugh KJ, et al. Influenza-induced type I interferon enhances susceptibility to gram-negative and gram-positive bacterial pneumonia in mice. Am J Physiol Lung Cell Mol Physiol. 2015;309:L158–L167.

114. Rynda-Apple A, Robinson KM, Alcorn JF. Influenza and bacterial superinfection: Illuminating the immunologic mechanisms of disease. Infect Immun. 2015;83:3764–3770.

115. Melvin JA, Bomberger JM. Compromised defenses: Exploitation of epithelial responses during viral-bacterial co-infection of the respiratory tract. PLoS Pathog. 2016;12:e1005797.

116. Siegel SJ, Roche AM, Weiser JN. Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. Cell Host Microbe. 2014;16: 55–67.

117. Hendricks MR, Lashua LP, Fischer DK, et al. Respiratory syncytial virus infection enhances *Pseudomonas aeruginosa* biofilm growth through dysregulation of nutritional immunity. Proc Natl Acad Sci. 2016;113:1642–1647.

118. Hennigar SR, McClung JP. Nutritional immunity: Starving pathogens of trace minerals. Am J Lifestyle Med. 2016;10: 170–173.

119. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. PLoS Pathog. 2012;8:e1002464.

120. Murray JF. Epidemiology of human immunodeficiency virus–associated pulmonary disease. Clin Chest Med. 2013;34:165–179.

121. Vittor AY, Garland JM, Gilman RH. Molecular diagnosis of TB in the HIV positive population. Ann Glob Health. 2014;80:476–485.

122. Tashiro M, Ciborowski P, Klenk H-D, Pulverer G, Rott R. Role of Staphylococcus protease in the development of influenza pneumonia. Nature. 1987;325:536–537.

123. Conenello GM, Zamarin D, Perrone LA, Tumpey T, Palese P. A single mutation in the PB1-F2 of H5N1 (HK/97) and 1918 influenza a viruses contributes to increased virulence. PLoS Pathog. 2007;3:1414–1421.

124. Chattoraj SS, Ganesan S, Jones AM, et al. Rhinovirus infection liberates planktonic bacteria from biofilm and increases chemokine responses in cystic fibrosis airway epithelial cells. Thorax. 2011;66:333–339.

125. Pettigrew MM, Marks LR, Kong Y, Gent JF, Roche-Hakansson H, Hakansson AP. Dynamic changes in the *Streptococcus pneumoniae* transcriptome during transition from biofilm formation to invasive disease upon influenza a virus infection. Infect Immun. 2014;82:4607–4619.

126. Chao Y, Marks LR, Pettigrew MM, Hakansson AP. *Streptococcus pneumoniae* biofilm formation and dispersion during colonization and disease. Front Cell Infect Microbiol. 2015;4:194.

127. di Mauro G, Cristina S, Concetta R, Francesco R, Annalisa C. SARS-Cov-2 infection: Response of human immune system and possible implications for the rapid test and treatment. Int Immunopharmacol. 2020;84:106519–106519.

128. Nikolich-Zugich J, Knox KS, Rios CT, et al. SARS-CoV-2 and COVID-19 in older adults: What we may expect regarding pathogenesis, immune responses, and outcomes. GeroScience. 2020;42(2):505–514.

129. Li CK-f, Xu X. Host immune responses to SARS coronavirus in humans. Molecular biology of the SARS-coronavirus, 2009; p. 259–278.

130. Frieman M, Baric R. Mechanisms of severe acute respiratory syndrome pathogenesis and innate immunomodulation. Microbiology and molecular biology reviews: MMBR 72, 672–685, Table of Contents, 2008.

131. Cinatl J, Morgenstern B, Bauer G, et al. Treatment of SARS with human interferons. Lancet (London, England). 2003;362: 293–294.

132. Spiegel M, Pichlmair A, Martinez-Sobrido L, et al. Inhibition of Beta interferon induction by severe acute respiratory syndrome coronavirus suggests a two-step model for activation of interferon regulatory factor 3. J Virol. 2005;79:2079–2086.

133. Haagmans BL, Kuiken T, Martina BE, Fouchier RA, Rimmelzwaan GF, et al. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat Med. 2004;10:290–293.

134. Freundt EC, Yu L, Park E, Lenardo MJ, Xu XN. Molecular determinants for subcellular localization of the severe acute respiratory syndrome coronavirus open reading frame 3b protein. J Virol. 2009;83:6631–6640.

135. Narayanan K, Huang C, Lokugamage K, et al. Severe acute respiratory syndrome coronavirus nsp1 suppresses host gene expression, including that of type I interferon, in infected cells. J Virol. 2008;82:4471–4479.

136. Devaraj SG, Wang N, Chen Z, et al. Regulation of IRF-3-dependent innate immunity by the papain-like protease domain of the severe acute respiratory syndrome coronavirus. J Biol Chem. 2007;282:32208–32221.

137. Krahling V, Stein DA, Spiegel M, Weber F, Muhlberger E. Severe acute respiratory syndrome coronavirus triggers apoptosis via protein kinase R but is resistant to its antiviral activity. J Virol. 2009;83:2298–2309.

138. Bezerra PG, Britto MC, Correia JB, Duarte MdCM, Fonceca AM, et al. Viral and atypical bacterial detection in acute respiratory infection in children under five years. PloS One. 2011;6:e18928.

139. Binks MJ, Cheng AC, Smith-Vaughan H, et al. Viral-bacterial co-infection in Australian indigenous children with acute otitis media. BMC Infect Dis. 2011;11:161.

140. Johansson N, Kalin M, Hedlund J. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. Scand J Infect Dis. 2011;43:609–615.

141. Edrada EM, Lopez EB, Villarama JB, Villarama EPS, Dagoc BF, et al. First COVID-19 infections in the Philippines: A case report. Trop Med Health. 2020;48:1–7.

142. Kaiser L, Regamey N, Roiha H, Deffernez C, Frey U. Human coronavirus NL63 associated with lower respiratory tract symptoms in early life. Pediatr Infect Dis J. 2005;24: 1015–1017.

143. Golda A, Malek N, Dudek B, et al. Infection with human coronavirus NL63 enhances streptococcal adherence to epithelial cells. J Gen Virol. 2011;92:1358–1368.

144. Dijkman R, Jebbink MF, El Idrissi NB, et al. Human coronavirus NL63 and 229E seroconversion in children. J Clin Microbiol. 2008;46:2368–2373.

145. Wang J-b, Xu N, Shi H-z, Huang X-z, Lin L. Organism distribution and drug resistance in 7 cases of severe acute respiratory syndrome death patients with secondary bacteria infection. Chin Crit Care Med. 2003;15:523–525.

146. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395:507–513.

147. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.

148. Zhang G, Hu C, Luo L, et al. Clinical features and outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol. 2020;127:104364.

149. Blasco ML, Buesa J, Colomina J, et al. Co-detection of respiratory pathogens in patients hospitalized with coronavirus viral disease-2019 pneumonia. J Med Virol. 2020.

150. Claire D, Rémi Le G, Claire T, et al. Panton-valentine Leukocidin–secreting *Staphylococcus aureus* pneumonia complicating COVID-19. Emerg Infect Dis J. 2020;26.

151. Bordi L, Nicastri E, Scorzolini L, et al. Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2), Italy, February 2020. Eurosurveillance. 2020;25:2000170.

152. Duployez C, Le Guern R, Tinez C, et al. Panton-valentine Leukocidin-secreting *Staphylococcus aureus* pneumonia complicating COVID-19. Emerg Infect Dis. 2020;26.

153. Fan BE, Lim KGE, Chong VCL, Chan SSW, Ong KH, Kuperan P. COVID-19 and *Mycoplasma pneumoniae* coinfection. Am J Hematol. 2020;95:723–724.

154. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: A retrospective, single-Centre, descriptive study. Lancet Infect Dis. 2020;20:559–564.

155. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020.

156. Chakraborty S. Metagenome of SARS-Cov2 patients in Shenzhen with travel to Wuhan shows a wide range of species-Lautropia, Cutibacterium, Haemophilus being most abundant-and Campylobacter explaining diarrhea, 2020.

157. Chakraborty S. The 2019 Wuhan outbreak could be caused by the bacteria Prevotella, which is aided by the coronavirus, possibly to adhere to epithelial cells-Prevotella is present in huge amounts in patients from both China and Hong Kong, 2020.

158. Chakraborty S. San Diego county Nanopore SARS-Cov2 sequencing data shows metagenomic Prevotella, *Haemophilus parainfluenzae*, a lot of unknown species and chimeric reads, 2020.

159. Chakraborty S. Metagenome of SARS-Cov2 from a patient in Brazil shows a wide range of bacterial species-Lautropia, Prevotella, Haemophilus-overshadowing viral reads, which does not even add up to a full genome, explaining false negatives, 2020.

160. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol. 2020;20:363–374.

161. MacIntyre CR, Chughtai AA, Barnes M, et al. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a(H1N1)pdm09. BMC Infect Dis. 2018;18:637–637.

162. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: Potentially lethal and unexplored in COVID-19. Lancet Microbe. 2020;1(1):e11.

163. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395:1054–1062.

164. Wu F, Zhao S, Yu B, et al. Complete genome characterisation of a novel coronavirus associated with severe human respiratory disease in Wuhan, China. bioRxiv. 2020.

165. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. Lancet Respir Med. 2020;8:506–517.

166. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;105949.

167. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr. 2020;14:241–246.

168. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. Lancet Respir Med. 2013;1:262–274.

169. Devaux, C, Colson P, Raoult D, Rolain J-M. Teicoplanin: An alternative drug for the treatment of coronavirus COVID-19. Int J Antimicrob Agents. 2020;(4):105944.

170. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: A retrospective observational study. Am J Respir Crit Care Med. 2020;201:1372–1379.

171. Willyard C. The drug-resistant bacteria that pose the greatest health threats. Nat News. 2017;543:15.

172. Hagan T, Cortese M, Rouphael N, et al. Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. Cell. 2019;178:1313–1328.e1313.

173. Kelly PN. Antibiotics blunt flu immunity. Science. 2019;366:197–198.

174. Birger RB, Kouyos RD, Cohen T, et al. The potential impact of coinfection on antimicrobial chemotherapy and drug resistance. Trends Microbiol. 2015;23:537–544.

175. Römling U, Balsalobre C. Biofilm infections, their resilience to therapy and innovative treatment strategies. J Intern Med. 2012;272:541–561.