# Chapter 11
# Unlocking the Mysteries of the Human Microbiome to Combat COVID-19

**Pushpanathan Muthuirulan, Meenakshi Bandyopadhyay, Sireesha Mamillapalli, and Pooja Sharma**

## 1 Introduction

The recent global dissemination of the novel coronavirus SARS-CoV-2 and the subsequent COVID-19 pandemic have galvanized the scientific community around the central goal of developing therapeutics for immediate and long-term treatment (Malinis et al. 2020; Shi et al. 2020; Pascarella et al. 2020; Shah et al. 2020). While global research efforts are being directed toward development of effective treatment strategies against COVID-19, the possible connection between the human microbiome and COVID-19, which may influence the outcome of the clinical manifestation, should be considered and investigated. Human-microbe associations and their roles in influencing host physiology and immunity have been well known since the early nineteenth century (Hooper et al. 2012; Belkaid and Hand 2014; Quigley 2013; Young 2017). Microbial evolution and colonization within the human host has led to the establishment of an important biological interface between human health and diseases (O'Hara and Shanahan 2006; Fan and Pedersen 2021). Humans

Pushpanathan Muthuirulan, Meenakshi Bandyopadhyay, Sireesha Mamillapalli and Pooja Sharma contributed equally with all other contributors.

P. Muthuirulan (✉)
Department of Human Evolutionary Biology, Harvard University, Cambridge, MA, USA
e-mail: muthuirulanp@fas.harvard.edu

M. Bandyopadhyay
Mithibai College, Mumbai, India

S. Mamillapalli
Geisinger Commonwealth School of Medicine, Scranton, Pennsylvania, USA

P. Sharma
Department of Biology, The Catholic University of American, Washington, DC, USA



S. Thomas (ed.), *Human Microbiome*,
https://doi.org/10.1007/978-981-16-7672-7_11

host a highly diverse group of microbes, which consists mainly of ecological communities of commensals, symbionts, and opportunistic pathogens that reside within different parts of the body, including the gastrointestinal tract (GI), to perform life-sustaining functions. Commensals and symbionts constitute a major portion of the diverse microbial group, while opportunistic pathogens are relatively few and less abundant. Commensals are beneficial to humans and they provide colonization resistance to pathogens (Thursby and Juge 2017; Dekaboruah et al. 2020).

A balance within the innate microbiota with reduced populations or complete elimination of pathogenic microbes is expected in a healthy individual (Belkaid and Hand 2014). The overall balance in the structure and composition of microbiota is important to ensure a healthy well-being and quality of life. Dysbiosis of the microbiota induced by certain risk factors such as infectious diseases, dietary changes, hypertension, cholesterol, diabetes, stress, aging, lack of physical activity, and use of antibiotics exerts a profound impact on human health (DeGruttola et al. 2016; Riccio and Rossano 2018; Frohlich et al. 2016). An overview of the relationships between microbial dysbiosis, risk factors, and COVID-19 disease is shown in Fig. 11.1. Several studies have demonstrated the remarkable association between human diseases and dysbiosis of the microbiota, and have shown that subtle alterations in the human microbiota can cause severe health complications such as diabetes, eczema, allergies, acne, diarrhea, autism, cancer, gastric ulcer, cardiovascular diseases, obesity, rheumatoid arthritis, muscular dystrophy, multiple sclerosis, and other disorders, suggesting that the microbiome may serve as a key regulator of human health and disease development (Kesh et al. 2020; Lee et al. 2018, 2019; Pascal et al. 2018; Saffouri et al. 2019; Pulikkan et al. 2018; Sheflin et al. 2014; Bruno et al. 2018; Lau et al. 2017; Amabebe et al. 2020; Correa et al. 2019; Picca et al. 2018; Kirby and Ochoa-Reparaz 2018). With an aim to circumvent an aggressive immunological response to pathogenic infections like COVID-19, a microbiome may be pivotal in maintaining a host physiology and immunity to prevent an array of excessive physiological reactions that eventually become detrimental to vital organs (e.g., lungs, heart among others) in the human body.

Certain additional factors, such as excessive use of antibiotics and dietary changes, have been proven to cause disruption of the human microbiome which serves as a major risk factor for the development of several diseases (Francino 2015; Vangay et al. 2015; Dudek-Wicher et al. 2018). An excessive use of antibiotics considerably disrupts the ecology of the human microbiome. Unlike the innate microbiome, dysbiotic microbiota possesses a relatively less potential to afford protection against pathogens that may result in serious health issues associated with metabolic, immunological, and developmental disorders. The excessive use of antibiotics may also accelerate the evolution of drug resistance (Francino 2015; Vangay et al. 2015; Dudek-Wicher et al. 2018; Neuman et al. 2018; Magana et al. 2020). Despite the fact that antibiotics do not treat or prevent viral infections like COVID-19, antibiotic usage during COVID-19 has dramatically increased, which may exacerbate the current global status of antimicrobial resistance. Diet is one of the key factors influencing the composition and diversity of the human microbiota (Brown et al. 2012; Hills Jr. et al. 2019; Chan et al. 2013). Further studies are necessary to examine the

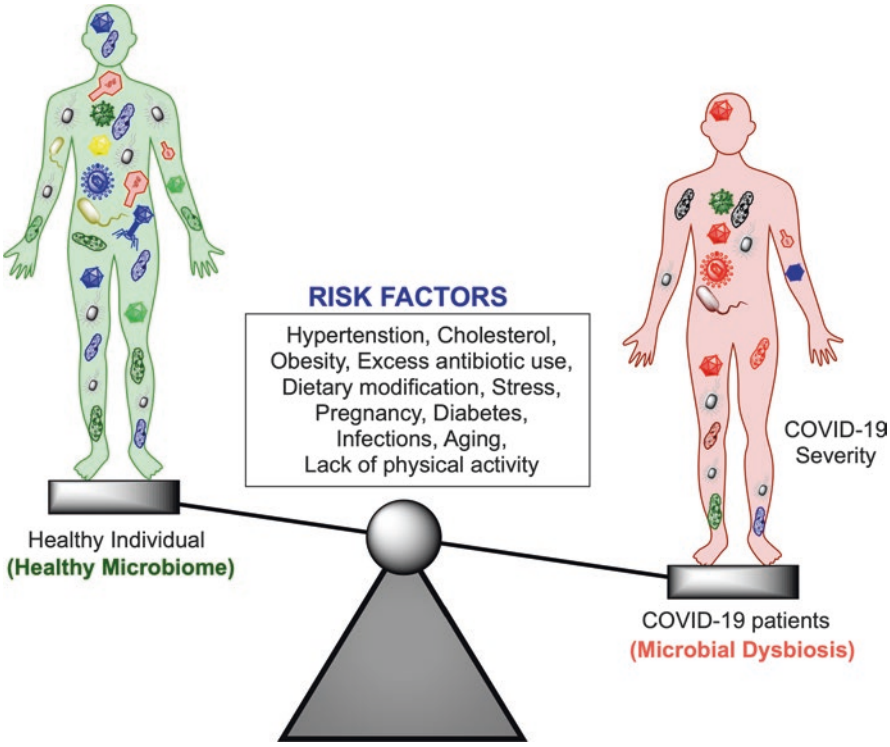


**Fig. 11.1** An overview of the relationships between microbial dysbiosis, risk factors, and COVID-19. Risk factors such as hypertension, cholesterol, obesity, diabetes, excessive use of antibiotics, stress, infections, aging, pregnancy, and lack of physical activity could induce microbial dysbiosis in humans which might contribute to the progression of COVID-19 disease

mechanisms by which dietary changes and lifestyle modifications during COVID-19 influence the composition of the human microbiome, which may indicate the potential of therapeutic dietary strategies used for modulation of the microbial composition, diversity, and stability in terms of preventing COVID-19. Pregnancy-induced microbial dysbiosis is often associated with cesarean delivery and is caused by complications, such as preterm birth, extremes of maternal body mass index (BMI), infection, extremes of infant size, and gestational diabetes (Neu and Rushing 2011). The inflammatory and immune changes mediated by pregnancy alter the maternal microbiome and contribute to long-term negative consequence for both the mother and child. Much remains to be discovered on this aspect; however, most studies are focused only on the healthy desired microbial changes during pregnancy. Future research is warranted to elucidate precise roles and mechanisms of the microbiota associated with pregnancy-related complications (Nuriel-Ohayon et al. 2016; Edwards et al. 2017).

A better understanding of the host-microbiome interaction is also important for the development of diagnostic approaches and for the treatment of diseases caused

by dysbiosis of the microbiota (Varghese et al. 2020; Casadevall and Pirofski 2000; Lebeer and Spacova 2019). Recent advances in high-throughput sequencing technologies offer deeper understanding of host-microbe interactions that can reveal the core characteristics of the microbiome interactions, including microbial identification, classification, profile prediction, and mechanisms of host-pathogen interaction, which will provide new avenues to gain deeper insights into the consequences of microbial imbalance with the potential to identify novel therapeutic drug targets or microbiome-mediated interventions for the treatment of COVID-19 (Baddal 2019; Hovhannisyan and Gabaldon 2019; Malla et al. 2018; Greenwood et al. 2016).

Here, we present an account of the existing knowledge linking the human microbiome to COVID-19 severity. The aim is to provide a foundation for exploration of the different aspects of the microbiome for the development of personalized interventions to treat or prevent COVID-19.

## 2 COVID-19-Associated Dysbiosis of the Host Microbiome

### *2.1 Gut Dysbiosis and COVID-19*

The human gut harbors a large repertoire of microorganisms and exerts a marked influence on host homeostasis and disease pathophysiology. Most microbial members of the gut predominantly belong to the phyla Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia (Konstantinidis et al. 2020; Ferreira et al. 2020; Kim et al. 2017). Gut dysbiosis induced by several risk factors has worsened human health, leading to the development of common respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), lung cancer, and other respiratory infections (Chunxi et al. 2020). COVID-19 patients also exhibit extrapulmonary distress, such as gastrointestinal tract infections and bleeding, vomiting, nausea, loss of appetite, abdominal pain/discomfort, diarrhea, and ulcerative colitis (Olaimat et al. 2020; From the American Association of Neurological Surgeons et al. 2018). Notably, the patients presenting with respiratory disorders are at increased risk, wherein a reduction in the population of *Lactobacillus* and *Bifidobacterium* has been observed, along with an increase in the number of opportunistic pathogens, thereby highlighting the negative effects exerted by microbial dysbiosis on pulmonary functions (Din et al. 2020; Ferreira et al. 2020).

Impaired gastrointestinal function and detection of the SARS-CoV-2 in stools of the affected individuals may hint at a fecal–oral route of transmission. Reports from the US and China highlight the SARS-CoV-2 multiplication ability in both respiratory and digestive tracts. Additionally, fecal samples obtained from infected patients showed the presence of the SARS-CoV-2 RNA even when respiratory samples showed the absence of the viral RNA. Thus, COVID-19 infection negatively affects the gastrointestinal (GI) tract and gut microbiota diversity. Studies also indicate that

the growth of opportunistic pathogens and reduction in the population of beneficial bacteria in the gut are positively correlated with the severity of COVID-19 infections (Olaimat et al. 2020). Based on meta-analysis reports of patients from Wuhan, 20% of the COVID-19 patients showed GI symptoms, including diarrhea. The SARS-CoV-2 virus has been detected in anal swabs and stool samples of almost 50% of the affected patients. The virus utilizes the angiotensin-converting enzyme 2 (ACE2) receptors for cellular entry and these receptors are reportedly expressed in respiratory and GI tracts, enterocytes, renal tubules, gallbladder, cardiomyocytes, male reproductive cells, placental trophoblasts, ductal cells, eye, and vasculature (Hikmet et al. 2020; Zuo et al. 2020).

The presence of *Collinsella aerofaciens*, *C. tanakaei, Streptococcus infantis,* and *Morganella morganii* has been reported in fecal samples of patients with a high burden of SARS-CoV-2 infection. On the contrary, fecal samples enriched with *Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii*, and Lachnospiraceae members demonstrated negligible or absence of the SARS-CoV-2 viral load. Notably, the elderly population is the most vulnerable group to COVID-19-associated mortality, and this may be attributed to the gut microbiota dysbiosis and impaired immune system usually observed in the elderly. Such a dysbiosis is also responsible for depression, increase in inflammatory markers, and development of cognitive deficits in the elderly individuals. Additionally, decrease in the Firmicutes to Bacteroidetes ratio and alterations in the abundance of Bacteroides, *Clostridium,* and *Lactobacillus* have been reported in the elderly. Thus, it can be implied that reduction in the gut microbial diversity may exacerbate the already impaired immune system which is observed in the elderly people, and this may increase mortality rates of such individuals (Villapol 2020). It can also be inferred that advancing age is a major factor responsible for gut microbiota dysbiosis, and measures should be undertaken to replenish the gut microbiota using microbiome-directed strategies.

COVID-19 has also threatened the mental health of the public, causing problems such as stress, panic, depression, anxiety, sleep disorders, lower mental well-being, and even suicide (Roy et al. 2020; Rajkumar 2020; Shinu et al. 2020). Mask wearing is another key precautionary measure that can protect us from contracting COVID-19 disease, but it can also provoke significant psychological responses that might cause life-long health consequences. One important aspect to be considered while discussing COVID-19-associated dysbiosis is the impact of psychological stress during the pandemic. It has been proven that the human gut microbiome plays an important role in human health and well-being, including mental health. Especially, the gut microbiota can cooperate with the hosts to regulate the development and function of the immune system, metabolic and nervous systems through dynamic bidirectional communication along the gut–brain axis. Disruption of microbial communities influencing central nervous system components (gut–brain axis) has been implicated in several neurological disorders (Morais et al. 2020). In addition, the COVID-19 pandemic has also caused decline in the physical health of individuals due to lack of exercise, ingestion of improper food, the effect of quarantine in the deterioration the mental health, which all can severely affect the human gut

microbial composition. Exercise is one of the best ways to optimize human physical and mental health, and lack of exercise during COVID-19 pandemic can put individuals at higher risk of infection. Prolonged exercise has beneficial effects and has been reported to increase intestinal permeability, compromising gut-barrier function and resulting in bacterial translocation from the colon (Peters et al. 2001; Gisolfi 2000). Probiotics have been reported to restore proper life balance and act as "psychobiotics," thereby serving as an alternate therapeutic option for COVID-19 (Rishi et al. 2020). The utilization of psychobiotics to manage serious problems related to psychological responses during this pandemic is almost unavoidable. Many microorganisms have been proposed as potential psychotropic agents to relieve anxiety and stress including *S. thermophiles*, *B. animalis*, *B. bifidum*, *B. longum*, *Lactobacillus bulgaricus*, *L. lactis*, *L. acidophilus*, *L. plantarum*, *L. reuteri*, *L. paracasei*, *L. helveticus*, *L. rhamnosus*, *Bacillus coagulans*, *Clostridium butyricum*, and others (de Araujo and Farias 2020). Recent evidence also hints at the mechanism by which high levels of stress increase gut permeability via increase in the corticotropin-releasing hormone levels, thereby altering gut microbial composition and leading to dysbiosis and possible susceptibility to SARS-CoV-2 infections (Anderson and Reiter 2020). Thus, focusing on the interaction of COVID-19 with gut–brain axis would allow us to evaluate the basic mechanisms involved in clinical manifestation of COVID-19 and would help endorse in the advancement of prophylactic and treatment strategies.

Social distancing is another key component of the expert-recommended guidelines to prevent the spread of SARS-CoV-2 infections. According to the World Health Organization, the transmission of SARS-CoV-2 virus primarily occurs through saliva or airborne respiratory droplets. Protective precautions to reduce the chances of being infected or spreading COVID-19 include wearing masks, hand sanitation, and social distancing from other people. Recent study has demonstrated the potential connection between social isolation and reduced bacterial diversity. Severe disruption of bacterial diversity caused by social distancing and other stress-related tension can lead to gut microbiota dysbiosis, which is associated with reduced numbers of protective bacteria. Such reduced numbers of protective bacteria can lead to higher risk of opportunistic infections and it has also been shown to increase the risk of influenza infections in the lung. Recent study has also suggested that a human microbiota can influence response to COVID-19, and that COVID-19 patients do possess increased risk of dysbiosis than healthy individual (Domingues et al. 2020). Further, the strict isolation and lockdown protocols implemented by different countries also play an important role in dysbiosis. While lockdown protocols were necessary for containment of the virus, this approach was observed to be a double-edged sword; as complete lack of human contact potentially reduces the dissemination of pathogens and helps to curb the pandemic, it also affects the microbial profile of an individual and reduces the microbial diversity, thereby increasing susceptibility to the SARS-CoV-2 owing to microbial dysbiosis (Domingues et al. 2020).

The involvement of gastrointestinal milieu in COVID-19 makes the gut microbiota a potential target in COVID-19 management and transmission (Chan et al.

2004). Moreover, COVID-19 infection is more severe among individuals with high blood pressure, diabetes, and obesity, conditions that are known to be associated with changes in the composition of the gut microbiota (Sattar et al. 2020; Rodgers and Gibbons 2020; Lim et al. 2021). Understanding the possible connections between the gut microbiota and COVID-19 severity would help to develop a novel and targeted approach to modulate harmful gut microbiota, that may represent a new therapeutic strategy against COVID-19 and its morbidities. Further, understanding of the host-microbial perturbations that underlie SARS-CoV-2 infections would also enable us to utilize the gut microbiota as an indicator for diagnosis of COVID-19 severity. Additionally, improving the composition of the gut microbiota and the proportion of metabolites produced therein through probiotics and personalized nutrition may enhance immunity and minimize the impact of COVID-19 severity in the elderly and immunocompromised patients (Olaimat et al. 2020).

In a study examining the role played by the gut microbiota in COVID-19 severity, a blood proteomic risk score (PRS) was used. Normal, non-infected susceptible individuals and patients with COVID-19 were screened using proteome data and via analysis of inflammatory biomarkers present in blood, to verify the PRS association with the risk of developing COVID-19 in healthy individuals. Studies on the core gut microbiota characteristics, such as gut microbiota metabolites produced and biosynthesis pathways involved, and fecal metabolomics were conducted. Demographics, lifestyle, and socioeconomic background of the patients and healthy individuals were also considered. The study demonstrated the involvement of the biosynthesis pathways for aminoacyl-tRNA, arginine, valine, leucine, and isoleucine, and highlighted the fact that alterations in the pathways could be used to differentiate between healthy and infected individuals, thereby indicating the utility of proteome data and inflammatory parameters to assess the severity of COVID-19 (Gou et al. 2020). Thus, tapping into the potential of the gut microbiome would help to identify potentially safe and affordable approaches for the prevention and treatment of COVID-19 and other viral respiratory diseases (Sadiq 2021; Donati Zeppa et al. 2020). However, more clinical and evidence-based trials are warranted to determine the appropriate strategy to fight against SARS-CoV-2 infections.

## *2.2 Lung Dysbiosis and Susceptibility to Viral Infections*

Lung microbiota is defined as the pulmonary microbial community that harbors a diverse group of microbes and is considered to be in close contact with the exogeneous microbes on a daily basis. This feature indicates that the lungs are one of the vital systems whose structure and functionality should be maintained for health and survival. The upper respiratory tract (URT) and lower respiratory tract (LRT) reportedly shelter similar microbial populations, although denser communities have been observed in the former versus the latter. The URT interconnected system predominantly consists of Actinobacteria (*Corynebacterium* and *Propionibacterium* species), Firmicutes (*Staphylococcus* species), Proteobacteria, and Bacteroidetes,

including *Streptococcus, Neisseria, Haemophilus*, and *Lachnospira* species. A commensal population including *Streptococcus pneumoniae, Neisseria meningitides*, and *Haemophilus influenzae* is native to the URT (Frank et al. 2010; Lemon et al. 2010; Bassis et al. 2014; Charlson et al. 2011; Yi et al. 2014; Ling et al. 2013; Allen et al. 2014). Microbial populations are relatively less diverse in the LRT (Dickson et al. 2017; Abreu et al. 2012; Bassis et al. 2015; Venkataraman et al. 2015), although phyla including Bacteroidetes and Firmicutes, which mainly include *Prevotella, Veillonella*, and *Streptococcus* species are found in lungs (Morris et al. 2013; Segal et al. 2013; Dickson et al. 2015). Relative abundance of certain species in LRT are often attributed to chronic airway diseases such as COPD and cystic fibrosis (Morris et al. 2013). Inadequate respiratory tract clearance due to increased mucus production and reduced ciliary beat frequency also leads to altered viral and bacterial clearance.

Influenza A virus (IAV) is known to cause flu infections posing a serious public health challenge, resulting in reduced annual workforce and an economic burden. Frequent antigenic substitution often referred to as an antigenic drift contributes to challenges in vaccine design. Alterations in healthy respiratory microbial populations are found to be associated with IAV infection. *Streptococcus* colonization, as evidenced in a mouse model, resulted in decreased susceptibility to IAV infection. Elevated H1 immunoglobulin (IgA) titers in an inoculation study of young adults by attenuated influenza vaccine were positively associated with *Streptococcus infantis* (Short et al. 2012; Diavatopoulos et al. 2010; McCullers and Rehg 2002). In contrast, *Prevotella* species abundance is associated with increased susceptibility to Influenza B viral infection, tuberculosis, and COPD. Children are more susceptible to IAV than young adults and varied reasons, including frequent exposure and lack robust immune development at young age, are attributed to the observed effect (Langevin et al. 2017; Hui et al. 2013; Cheung et al. 2013). Earlier study has demonstrated that pretreatment of mice with antibiotics disrupts the innate and adaptive immune systems (Ichinohe et al. 2011). It has also been reported that an altered microbiome results in the loss of lipopolysaccharides and pattern recognition receptors for activation of toll-like receptors and it thus reduces immune action by type I and II interferons (Ichinohe et al. 2011; Abt et al. 2012). Immunity is at the forefront in discerning the severity of the disease. Though several studies indicate a relationship between microbial populations and viral infections, comprehensive interventions involving animal and human subjects remain to be conducted to address the true effect of the respiratory microbiome and its susceptibility to viral infections and to exclude an altered immune response (Khatiwada and Subedi 2020).

Lung microbiome has received greater attention in recent times due to its association with immunity and respiratory diseases, including COVID-19. Lung microbiome plays an important role in activating an innate and adaptive immune response, which can potentially reduce the risk and consequences of COVID-19 (Khatiwada and Subedi 2020). Only a few studies have examined the relationship between COVID-19 and the lung microbiome. Shen et al. investigated the bronchoalveolar lavage fluid and found significant difference in microbial composition between COVID-19 patients and healthy control. COVID-19 patients showed enrichment of

pathogenic bacteria indicating, the degree of microbial imbalance in diseased states (Shen et al. 2020). In another study, Fan et al. have investigated the lung microbiome from the lung post-mortem biopsies from deceased COVID-19 patients. This study has reported the presence of most common bacterial (*Acinetobacter, Chryseobacterium, Burkholderia, Brevundimonas, Sphingobium*, and *Enterobacteriaceae*) and fungal genera (*Cutaneotrichosporon, Issatchenkia, Wallemia, Cladosporium, Alternaria, Dipodascus, Mortierella, Aspergillus, Naganishia, Diutina,* and *Candida*), indicating that bacterial and fungal infections are prevalent in COVID-19 patients (Fan et al. 2020). Overall, there is less substantial information available to explains the relationship between lung microbiome and COVID-19. Further studies are required to understand the role of lung microbiome in COVID-19 severity.

The gut and the lungs are the dominant locations for hosting the microbiota; however, the gut microbiota diversity and microbial population are remarkably higher than those observed in the lungs. Evidence indicates the presence of the gut–lung axis and a bidirectional crosstalk between the gut and the lungs. It has been hypothesized that inflammation of the gut also leads to lung inflammation through this axis. According to previous reports, it has been observed that the gut microbiome dysbiosis is linked with several respiratory disorders; further, in several respiratory diseases, the lung microbiota composition shifts toward the gut microbiota. Several factors have been proposed for this phenomenon. One of the factors hints at migration of the gut microbiota toward the lungs owing to increased permeability of the GI tract (Olaimat et al. 2020). To date, there is no direct evidence that describes the role of the lung microbiome in influencing COVID-19; however, related human and animal studies have shown that the human microbiome can play critical role in immune response development against viral infections. Future studies are necessary to investigate the relationship between the lung microbiome and COVID-19.

## *2.3 Pregnancy, Human Microbiota, and COVID-19*

The inflammatory and immune changes mediated by pregnancy alter maternal gut function and microbial composition. The maternal gut microbiome composition significantly contributes to obstetric outcomes with long-term health consequences for both the mother and the child. The hormones such as estrogen and progesterone contribute to a shift in the human microbiota and impact gut function, especially during the prenatal period (Edwards et al. 2017). Several studies have shown that the microbiome can be vertically transmitted from parents to offspring, and it is plausible that the maternal–infant microbiome transfer may influence the early stages of infant health (Yang et al. 2016; Dunn et al. 2017). The overall risk of developing complications associated with COVID-19 in pregnant women is low (Maleki Dana et al. 2020). However, recent data highlight the increased risk for severe COVID-19 during pregnancy. According to the Centers for Disease Control and Prevention (CDC), pregnant women are 5.4 times more likely to be

hospitalized, 1.5 times more likely to be subjected to intensive care, and 1.7 times more likely to require mechanical ventilation than non-pregnant women (Zambrano et al. 2020). Certain studies suggest that premature birth is more likely to be observed in pregnant women with COVID-19 and their babies are more likely to be admitted to a neonatal unit (Maleki Dana et al. 2020; Yang et al. 2020). One study has suggested that newborns rarely acquire COVID-19 from SARS-CoV-2 positive or suspected SARS-CoV-2-infected mothers. Over 800 newborns reported, the incidence of vertical transmission has proven to be low, indicating that adverse clinical outcomes in newborn seem to be due to maternal disease status in the small subset of newborns with critically ill mothers, rather than illness due to SARS-CoV-2 infection (Kyle et al. 2020). One another study has confirmed that COVID-19 infection in pregnant women resembles the SARS-CoV-2 infection in non-pregnant adult population, with possibly less chance for adverse maternal or perinatal outcome (Elshafeey et al. 2020). All these studies suggest that there is no vertical transmission of COVID-19 from the mother to the fetus; however, certain studies indicate such a pattern of transmission, but additional convincing evidence regarding the same remains to be reported (Dashraath et al. 2020; Chen et al. 2020). Further studies are necessary to understand the COVID-19-mediated microbiome alteration and maternal microbial transmission during pregnancy which may help explain the mechanisms of microbiome alterations associated with COVID-19 that impact fetal growth and development.

## 3 Antimicrobial Resistance in the Era of COVID-19

### *3.1 Host Gut Microbiome Dysbiosis Exacerbated by Use of Antibiotics*

Excessive and long-term use of antibiotics can trigger microbiome dysbiosis. Studies on vancomycin have reported long-lasting shifts in the gut microbiome, with expansion of less abundant bacterial populations (Kim et al. 2017). It has been reported that excessive antibiotic usage can lead to altered GI tract anatomy and physiology; this may play a role in the migration of gut microbes toward the lungs and lead to altered microbial diversity (Olaimat et al. 2020)**.** Considerable evidence has demonstrated an association between antibiotic usage during the first year of life and development of asthma by the 6th–7th year of life (Becattini et al. 2016). A recent study has shown that antibiotic-naive patients with COVID-19 demonstrated presence of bacteremia-causing opportunistic pathogens, such as *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii* compared to healthy individuals. Antibiotic-treated COVID-19 patients showed depletion of beneficial microbes including *Faecalibacterium prausnitzii*, *Lachnospiraceae bacterium 5_1_63FAA, Eubacterium rectale, Ruminococcus obeum*, and *Dorea formicigenerans* compared with antibiotic-naive patients with COVID-19. Bacteroides species, including *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides*

*massiliensis*, and *Bacteroides ovatus*, showed inverse correlation with the fecal SARS-CoV-2 load; notably, these species were associated with decreased ACE2 expression in the murine colon, indicating that *Bacteroides* species might play a protective role in combating SARS-CoV-2 through ACE2 expression. The highest SARS-CoV-2 mortality and morbidity rates have been reported in older patients and in those with underlying comorbidities. Notably, a less abundant population of the *Bacteroides* species was observed in such patients, indicating that an individual's gut microbiome might affect the immunological response to SARS-CoV-2 infection (Zuo et al. 2020).

## *3.2 Antibiotic Prescription, Over-sanitation, and Antimicrobial Resistance During the COVID-19 Pandemic*

With regard to symptomatic cases, individuals infected with the SARS-CoV-2 usually present with fever, respiratory distress, and pneumonia; in extreme cases, they present with multiple gastrointestinal, renal, neurological, and cardiac issues, wherein hospitalization is deemed necessary (Ferreira et al. 2020). Generally, individuals exhibiting upper or lower respiratory tract diseases are prescribed with antibiotics. However, as per findings of a recent study, 72% of the patients received antibiotics, among which only 8% were diagnosed with bacterial or fungal co-infections. As per WHO reports, treatments using azithromycin and hydroxychloroquine have been rampantly prescribed irrespective of any conclusive evidence from COVID-19 clinical trials. Considering the indiscriminate and injudicious use of antibiotics during COVID-19, which may lead to subsequent development of antimicrobial resistance, the WHO has outlined specific antibiotic usage guidelines along with antibiotic stewardship principles. In the absence of any underlying bacterial infection, the guidelines explicitly deter individuals from opting for an antibiotic therapy or antibiotic-mediated prophylaxis for moderate COVID-19 symptoms. The guidelines also recommend consideration of epidemiology, host factors, and routine clinical assessments prior to antibiotic prescription. Only older patients residing in long-term care facilities and children below 5 years of age exhibiting moderate COVID-19 symptoms can be treated with antibiotics prescribed for bacterial pneumonia (Getahun et al. 2020).

Increased mortality rates of patients with COVID-19 seem to be associated with excessive antibiotic usage and gut microbial dysbiosis (Din et al. 2020). A majority of the respiratory tract infection (RTI) cases are erroneously treated with antibiotics, regardless of the presence of a bacterial etiology. Considering this, the Choosing Wisely campaigns have been initiated to disseminate appropriate information on antibiotic usage. The campaigns propagate avoidance of antibiotic usage in cases of viral origin (influenza-like illness), upper respiratory infections, and self-limiting sinusitis. A recent study has further proposed that COVID-19/influenza-like symptoms and common cold cases should not be treated with antibiotics or symptomatic

management is sufficient; further examination, in-person visits, bacterial culture tests, vital sign abnormalities, and increase/decrease in symptoms should be considered before prescribing antibiotics for acute otitis media, pharyngitis, sinusitis, COPD, and suspected pneumonia cases (Leis et al. 2020).

A recent study conducted on the antibiotic usage in the initial period of the COVID-19 pandemic reported a biphasic pattern. Antibiotic prescription and consumption increased through March and April 2020. In March 2020, during the first peak, amoxicillin/clavulanate was recommended for patients with COVID-19 and administration or prescription of antibiotics increased gradually. In April 2020, during the second peak, broad-spectrum antibiotics (cefepime, piperacillin/tazobactam, meropenem, imipenem, and ertapenem) were prescribed with reduced prescription of amoxicillin/clavulanate. The first peak and antibiotic prescription pattern coincided with increased hospitalization rates. The second peak coincided with increase in severity of cases and probable development of nosocomial infections, thereby demonstrating increased prescription of broad-spectrum antibiotics (Abelenda-Alonso et al. 2020).

To provide a more accurate explanation of antimicrobial resistance, the term "resistome" is frequently used. The resistome comprises antimicrobial resistance genes (ARGs) of the pathogenic and non-pathogenic gut bacteria. The dissemination of ARGs via horizontal gene transfer and mobile genetic elements increases the risk of antimicrobial resistance within the intestinal microbiome (Konstantinidis et al. 2020). The risk is increased further with consumption of antibiotics. In a study involving pigs fed with a diet supplemented with antibiotics, findings showed that ARG abundance increased in the porcine microbiota, which led to the development of tolerance against drugs to which they were not exposed. In another study, it was observed that approximately 40% of the bacterial members within hosts harbored quinolone-resistance genes, even in those who had never been exposed to the drugs. In a study involving Finnish children, early use of macrolides demonstrated a microbial profile in which depletion of Actinobacteriaceae and an increased population of Bacteroidetes and Proteobacteria was observed along with ARG induction (Becattini et al. 2016).

Since use of disinfectant and over-sanitation have the capacity to alter the microbial diversity, increased exposure to hand sanitizer, disinfectants, and household cleaning products during this pandemic could be associated with disturbance of human microbiota. Moreover, the emerging links between over-sanitization and occurrence of non-communicable diseases and antimicrobial resistance have involved the human microbiome. The disruption of gut microbiota induced by disinfectants and over-sanitation have life-long health consequences. Regarding the evidence-based reduction in exposure to non-pathogenic commensal bacteria and gut dysbiosis, further study is warranted to investigate the effects of massive use of disinfectants or sanitizers during the COVID-19 pandemic. In this context, recommendations to consume probiotics, pychobiotics, and fermented foods might reverse the consequences by alleviating dysbiosis (Ejtahed et al. 2020). Altogether, the above-mentioned findings highlight the importance of judicious use of antibiotics, hand sanitizer, and household cleaning products to curb antimicrobial resistance

and microbial dysbiosis, which many seem to consider as a collateral damage of the COVID-19 pandemic.

## 4 Dietary Changes and Human Microbiota

Diet is one of the most important regulators of the human microbiome; however, the precise mechanisms by which diet induces microbiome variations remain elusive. Health benefits attained by following an optimal diet are evident as per previous findings and also provide a concrete foundation for leading a healthy lifestyle in the future. The COVID-19 pandemic has affected the global population, thereby emphasizing the need for awareness among communities to adopt safe practices in terms of food hygiene and consumption. Several governmental and non-governmental organizations have recognized the necessity of specific guidelines for the prognosis of COVID-19. A recent study has reported that implementation of the lockdown during COVID-19 has resulted in the practice of consumption of home-cooked, healthy meals that enrich beneficial microflora in the gut, which may have resulted in better prognosis of COVID-19 patients in India compared to those in western countries (Rishi et al. 2020). Nutritional modulation is vital for individuals of different ages, with chronic health conditions, and for therapy and management of several health issues. Nutritional excess or deficiency has been associated with immunodeficiency, and therefore adequate nutrition is critically important for homeostasis and for optimal functioning of the immune system to fight against SARS-CoV-2 infection, as well as for the development of an efficient immune system to combat other pathogenic viruses and microorganisms (Chaari et al. 2020).

Considerable cultural and geographical differences also play a role in varied global food consumption patterns, thereby making nutritional optimization a challenging yet a necessary task. Several dietary recommendations were made during the initial phases of the pandemic and have been implemented as a part of the treatment and prevention strategy against COVID-19. Fresh fruits and vegetables rich in nutrients and water were recommended by most studies to boost the intake of micronutrients. Vitamins and minerals contribute toward healthy maintenance of physical barrier organs including the skin, mucus membrane, respiratory tract, and gastrointestinal tract to prevent viral infections. Vitamins A, C, D, E, B6, and B12 help to maintain cell division, proliferation, and functional aspects of immune cells. They provide support in inflammatory response and antibody production of T and B cells (https://www.eufic.org/en/food-safety). A special emphasis has been laid on vitamins C and D, supporting the significance of the former in individuals who are at risk of developing respiratory tract infections. Antioxidant properties of both vitamins C and D have been well established in lowering the pulmonary-associated infections. Vitamin D status is also associated with the severity of COVID-19 (McCartney and Byrne 2020; Mansur 2020). Minerals such as zinc and selenium are known to exhibit antioxidant properties as evidenced by suppression of oxidative stress and augmentation of host immune responses (Beck et al. 2003; Read et al.

2019; Lee 2018). Mice with selenium deficiency subjected to influenza viral challenge showed an enhanced pathology in the lungs (Beck et al. 2003). Adequate hydration is necessary for maintaining body homeostasis, kidney function, appropriate cognitive senses, and cardiovascular function (El-Sharkawy et al. 2015). Hypohydration leads to exhibition of adverse health effects over varying age groups. Gut commensal populations like *Bifidobacterium* and *Lactobacillus* and pathogenic bacteria like *Bacteroides fragilis* and *Clostridium perfringens* were shown to be increased and decreased respectively via consumption of whey and pea protein extracts (Swiatecka et al. 2011). Consumption of whole-grain food rich in non-digestible carbohydrates reduced proinflammatory cytokines IL-6 and insulin resistance (Keim and Martin 2014). Increased levels of IL-10 (an anti-inflammatory cytokine) were observed with the intake of butyrated maize starch (West et al. 2017). Fermented foods rich in live microorganisms *Lactobacillus* and *Bifidobacterium* that include many different strains such as *L. fermentum, L. reuteri, L. paracasei, L. rhamnosus, L. acidophilus, L. plantarum, B. longum, B. breve, B. bifidum*, and *B. animalis* were shown to reduce enteropathogens *E. coli* and *Helicobacter pylori* (Yang and Sheu 2012). Treg cells, which are downregulators of allergic response, were shown to be induced by consumption of probiotics (Feleszko et al. 2007). It has been demonstrated that diet-microbiome interactions are personalized, suggesting that diet-microbiome studies should either include longitudinal sampling within individuals to identify personalized responses to dietary changes or should consider adequate number of participants spanning a wide range of microbiome types to study more generalized responses (Johnson et al. 2020). Although the dietary guidelines for the COVID-19 pandemic represent generic information based on healthy personnel, it would be beneficial to formulate dietary recommendations based on patients' requirements. A range of tolerable intake levels of nutrients with respect to varied chronic conditions are desirable to provide specific information rather than a "one-size-fits-all" approach. However, extensive research should be performed to understand the role of dietary changes on human microbiome alterations to develop better diagnosis and therapeutic dietary strategies for COVID-19 patients.

## 5 Microbiome-Based Interventions

Host-microbe interactions play a key role in determining the health and disease status in humans. Microbial imbalance is related to a plethora of diseases, including COVID-19. A better understanding of the host-microbe interaction is important to develop efficient diagnosis and treatment strategies for these ailments (Varghese et al. 2020; Casadevall and Pirofski 2000; Lebeer and Spacova 2019). By precisely modulating the host microbiome, either by removing the pathogenic taxa or by reintroducing missing beneficial taxa, development of new therapeutic approaches for treatment of diseases associated with the dysbiosis of microbiota can be realized. Culturing of large microbial communities in the laboratory is impossible using traditional microbiology approaches. Consequently, it is difficult to comprehensively

profile individual microbes comprising a specific microbiome, and to understand their complex, multipartite interactions (Forbes et al. 2017). Microbiome-based interventions should be considered to formulate strategies in the source tracking and monitoring of microbial communities. Tools such as FEAST, PHASTER, PHASTEST, and Source Tracker are utilized to conduct source tracking to determine the origins of microbial agents, especially those implicated in diseases. In a previous study based on analysis of sequencing datasets of fecal samples obtained from patients with COVID-19, highlighting alterations of the gut microbiota, FEAST was used to conduct source tracking of the patients, and the results showed extremely high accuracy of source tracking. Thus, using such approaches, the microbiome can be used to determine sources and patterns of dissemination, divergence, and variations of pathogens (Han et al. 2020).

The structure of the microbial community observed in patients with COVID-19 and those with community-acquired pneumonia is reportedly similar. The oral microbiota and its dysbiosis have been implicated in multiple diseases, including COVID-19, type 2 diabetes, hypertension, and cardiovascular disease; notably, the comorbidities mentioned herein increase the risk of COVID-19-associated mortality. Modulation of the human gut microbiota diversity has been reported to ameliorate conditions like enteritis and ventilator-associated pneumonia. These findings indicate the crucial role played by the microbiome in various diseases and the potential of the microbiome to be altered to mitigate disease conditions. Apart from the microbiome, probiotics have garnered considerable attention to combat COVID-19. Several studies have highlighted the role of probiotics in reduction of serum lipid levels and augmentation of immunity; thus, probiotic-based approaches may be used to modulate the host microbiome and to elicit a remarkable immune response against SARS-CoV-2. Maintaining a moderate exercise regimen may also be beneficial to maintain the homeostasis of the gut microbiome (Han et al. 2020).

Recent advances in the next-generation sequencing (NGS) technology and availability of state-of-the-art bioinformatics tools have enabled investigation of the microbiome, defying the need for cultivation (Hiergeist et al. 2015). NGS is now becoming a mainstream option for most researchers in the fight against the viral pandemic and they provide key insights into comprehensive structure of the microbiome and microbiome-host metabolic signal disruption in humans that would help us gain advanced knowledge on the impact of microbial imbalance and the role of microbial communities in human health and diseases. Several methods such as 16S rRNA sequencing and metagenome shotgun sequencing are available to explore the structural and functional composition of human microbiome. OMICs technologies (transcriptomics, proteomics, and metabolomics) offer newfound analytical opportunities to understand the mechanisms by which these microbial communities function and relate to their environment (Jiang et al. 2019; Hiergeist et al. 2015). Utilization of these technologies in COVID-19 research will improve our ability to rapidly and reproducibly characterize the microbial changes associated with COVID-19 severity, and it also offers an opportunity to develop fundamentally new diagnostic biomarkers (microbiome signatures) and therapeutics for COVID-19 (Fig. 11.2).


**Fig. 11.2** Strategies for development of personalized therapy to treat COVID-19. Utilization of OMICS technologies in COVID-19 research will improve our ability to investigate microbial changes associated with COVID-19 severity and offers an opportunity to develop personalized therapeutics for the treatment of COVID-19

## 6 Conclusion

Based on the above-mentioned information, it can be inferred that the human microbiome can have a profound impact on the susceptibility to SARS-CoV-2 infection and COVID-19 severity. The involvement of gastrointestinal symptoms and respiratory illness in COVID-19 makes the gut and lung microbiota a potential target in COVID-19 management. In addition, public health actions such as social distancing, mask wearing, quarantine, and lack of physical activities have threatened the

mental health of the public which impose major negative impact on the human microbiome. The hope is that the new class of medicines "psychobiotics" will eventually provide powerful treatment for depression and other mental illness that arise during this pandemic. Pregnant women are at increased risk of developing complications due to COVID-19; however, risk of neonatal infection via perinatal/postnatal transmission is low, suggesting that vertical transmission of microbiome from infected mother to newborn may not affect the fetal growth and development. This is one area where further study is warranted. Besides these, dietary changes, lifestyle modification, over-sanitation, and excessive use of antibiotics during this pandemic can cause severe microbiota dysbiosis. In this context, recommendations to consume probiotics, pychobiotics, fermented foods, and judicious use of antibiotics/disinfectant might reverse the consequences by alleviating dysbiosis. Thus, the microbiome is a key regulator of human health and diseases and it is essentially important for us to protect our microbiome from harmful risk factors to promote disease-free life. Future studies should investigate the human microbiome and correlate findings with the severity of COVID-19. Identification of the beneficial and harmful microbial components and their roles in early development of disease may help in the design of novel strategies for alteration of the microbiota to reduce disease severity. We are therefore confident that future microbiome studies will provide useful clinical knowledge, as well as offer a broader understanding of COVID-19 progression which will aid in the development of necessary tools and approaches to better diagnose, treat, and prevent this disease.

## References

Abelenda-Alonso G, Padulles A, Rombauts A, Gudiol C, Pujol M, Alvarez-Pouso C, Jodar R, Carratala J (2020) Antibiotic prescription during the COVID-19 pandemic: a biphasic pattern. Infect Control Hosp Epidemiol 41(11):1371–1372. https://doi.org/10.1017/ice.2020.381

Abreu NA, Nagalingam NA, Song Y, Roediger FC, Pletcher SD, Goldberg AN, Lynch SV (2012) Sinus microbiome diversity depletion and Corynebacterium tuberculostearicum enrichment mediates rhinosinusitis. Sci Transl Med 4(151):151ra124. https://doi.org/10.1126/scitranslmed.3003783

Abt MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, Sonnenberg GF, Paley MA, Antenus M, Williams KL, Erikson J, Wherry EJ, Artis D (2012) Commensal bacteria calibrate the activation threshold of innate antiviral immunity. Immunity 37(1):158–170. https://doi.org/10.1016/j.immuni.2012.04.011

Allen EK, Koeppel AF, Hendley JO, Turner SD, Winther B, Sale MM (2014) Characterization of the nasopharyngeal microbiota in health and during rhinovirus challenge. Microbiome 2:22. https://doi.org/10.1186/2049-2618-2-22

Amabebe E, Robert FO, Agbalalah T, Orubu ESF (2020) Microbial dysbiosis-induced obesity: role of gut microbiota in homoeostasis of energy metabolism. Br J Nutr 123(10):1127–1137. https://doi.org/10.1017/S0007114520000380

Anderson G, Reiter RJ (2020) COVID-19 pathophysiology: interactions of gut microbiome, melatonin, vitamin D, stress, kynurenine and the alpha 7 nicotinic receptor: treatment implications. Melatonin Res 3(3):322–345. https://doi.org/10.32794/mr11250066

Baddal B (2019) Next-generation technologies for studying host-pathogen interactions: a focus on dual transcriptomics, CRISPR/Cas9 screening and organs-on-chips. Pathog Dis 77(6). https://doi.org/10.1093/femspd/ftz060

Bassis CM, Erb-Downward JR, Dickson RP, Freeman CM, Schmidt TM, Young VB, Beck JM, Curtis JL, Huffnagle GB (2015) Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. mBio 6(2):e00037. https://doi.org/10.1128/mBio.00037-15

Bassis CM, Tang AL, Young VB, Pynnonen MA (2014) The nasal cavity microbiota of healthy adults. Microbiome 2:27. https://doi.org/10.1186/2049-2618-2-27

Becattini S, Taur Y, Pamer EG (2016) Antibiotic-induced changes in the intestinal microbiota and disease. Trends Mol Med 22(6):458–478. https://doi.org/10.1016/j.molmed.2016.04.003

Beck MA, Levander OA, Handy J (2003) Selenium deficiency and viral infection. J Nutr 133(5 Suppl 1):1463S–1467S. https://doi.org/10.1093/jn/133.5.1463S

Belkaid Y, Hand TW (2014) Role of the microbiota in immunity and inflammation. Cell 157(1):121–141. https://doi.org/10.1016/j.cell.2014.03.011

Brown K, DeCoffe D, Molcan E, Gibson DL (2012) Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. Nutrients 4(8):1095–1119. https://doi.org/10.3390/nu4081095

Bruno G, Rocco G, Zaccari P, Porowska B, Mascellino MT, Severi C (2018) Helicobacter pylori infection and gastric Dysbiosis: can probiotics administration be useful to treat this condition? Can J Infect Dis Med Microbiol 2018:6237239. https://doi.org/10.1155/2018/6237239

Casadevall A, Pirofski LA (2000) Host-pathogen interactions: basic concepts of microbial commensalism, colonization, infection, and disease. Infect Immun 68(12):6511–6518. https://doi.org/10.1128/iai.68.12.6511-6518.2000

Chaari A, Bendriss G, Zakaria D, McVeigh C (2020) Importance of dietary changes during the coronavirus pandemic: how to upgrade your immune response. Front Public Health 8:476. https://doi.org/10.3389/fpubh.2020.00476

Chan KH, Poon LL, Cheng VC, Guan Y, Hung IF, Kong J, Yam LY, Seto WH, Yuen KY, Peiris JS (2004) Detection of SARS coronavirus in patients with suspected SARS. Emerg Infect Dis 10(2):294–299. https://doi.org/10.3201/eid1002.030610

Chan YK, Estaki M, Gibson DL (2013) Clinical consequences of diet-induced dysbiosis. Ann Nutr Metab 63(Suppl 2):28–40. https://doi.org/10.1159/000354902

Charlson ES, Bittinger K, Haas AR, Fitzgerald AS, Frank I, Yadav A, Bushman FD, Collman RG (2011) Topographical continuity of bacterial populations in the healthy human respiratory tract. Am J Respir Crit Care Med 184(8):957–963. https://doi.org/10.1164/rccm.201104-0655OC

Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, Li J, Zhao D, Xu D, Gong Q, Liao J, Yang H, Hou W, Zhang Y (2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 395(10226):809–815. https://doi.org/10.1016/S0140-6736(20)30360-3

Cheung MK, Lam WY, Fung WY, Law PT, Au CH, Nong W, Kam KM, Kwan HS, Tsui SK (2013) Sputum microbiota in tuberculosis as revealed by 16S rRNA pyrosequencing. PLoS One 8(1):e54574. https://doi.org/10.1371/journal.pone.0054574

Chunxi L, Haiyue L, Yanxia L, Jianbing P, Jin S (2020) The gut microbiota and respiratory diseases: new evidence. J Immunol Res 2020:2340670. https://doi.org/10.1155/2020/2340670

Correa JD, Fernandes GR, Calderaro DC, Mendonca SMS, Silva JM, Albiero ML, Cunha FQ, Xiao E, Ferreira GA, Teixeira AL, Mukherjee C, Leys EJ, Silva TA, Graves DT (2019) Oral microbial dysbiosis linked to worsened periodontal condition in rheumatoid arthritis patients. Sci Rep 9(1):8379. https://doi.org/10.1038/s41598-019-44674-6

Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C, Su LL (2020) Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol 222(6):521–531. https://doi.org/10.1016/j.ajog.2020.03.021

de Araujo FF, Farias DP (2020) Psychobiotics: an emerging alternative to ensure mental health amid the COVID-19 outbreak? Trends Food Sci Technol 103:386–387. https://doi.org/10.1016/j.tifs.2020.07.006

DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E (2016) Current understanding of Dysbiosis in disease in human and animal models. Inflamm Bowel Dis 22(5):1137–1150. https://doi.org/10.1097/MIB.0000000000000750

Dekaboruah E, Suryavanshi MV, Chettri D, Verma AK (2020) Human microbiome: an academic update on human body site specific surveillance and its possible role. Arch Microbiol 202(8):2147–2167. https://doi.org/10.1007/s00203-020-01931-x

Diavatopoulos DA, Short KR, Price JT, Wilksch JJ, Brown LE, Briles DE, Strugnell RA, Wijburg OL (2010) Influenza a virus facilitates Streptococcus pneumoniae transmission and disease. FASEB J 24(6):1789–1798. https://doi.org/10.1096/fj.09-146779

Dickson RP, Erb-Downward JR, Freeman CM, McCloskey L, Beck JM, Huffnagle GB, Curtis JL (2015) Spatial variation in the healthy human Lung microbiome and the adapted island model of Lung biogeography. Ann Am Thorac Soc 12(6):821–830. https://doi.org/10.1513/AnnalsATS.201501-029OC

Dickson RP, Erb-Downward JR, Freeman CM, McCloskey L, Falkowski NR, Huffnagle GB, Curtis JL (2017) Bacterial topography of the healthy human lower respiratory tract. mBio 8(1). https://doi.org/10.1128/mBio.02287-16

Din AU, Mazhar M, Waseem M, Ahmad W, Bibi A, Hassan A, Ali N, Gang W, Qian G, Ullah R, Shah T, Ullah M, Khan I, Nisar MF, Wu J (2020) SARS-CoV-2 microbiome dysbiosis linked disorders and possible probiotics role. Biomed Pharmacother 133:110947. https://doi.org/10.1016/j.biopha.2020.110947

Domingues CPF, Rebelo JS, Dionisio F, Botelho A, Nogueira T (2020) The social distancing imposed to contain COVID-19 can affect our microbiome: a double-edged sword in human health. mSphere 5(5). https://doi.org/10.1128/mSphere.00716-20

Donati Zeppa S, Agostini D, Piccoli G, Stocchi V, Sestili P (2020) Gut microbiota status in COVID-19: an unrecognized player? Front Cell Infect Microbiol 10:576551. https://doi.org/10.3389/fcimb.2020.576551

Dudek-Wicher RK, Junka A, Bartoszewicz M (2018) The influence of antibiotics and dietary components on gut microbiota. Prz Gastroenterol 13(2):85–92. https://doi.org/10.5114/pg.2018.76005

Dunn AB, Jordan S, Baker BJ, Carlson NS (2017) The maternal infant microbiome: considerations for labor and birth. MCN Am J Matern Child Nurs 42(6):318–325. https://doi.org/10.1097/NMC.0000000000000373

Edwards SM, Cunningham SA, Dunlop AL, Corwin EJ (2017) The maternal gut microbiome during pregnancy. MCN Am J Matern Child Nurs 42(6):310–317. https://doi.org/10.1097/NMC.0000000000000372

Ejtahed HS, Hasani-Ranjbar S, Siadat SD, Larijani B (2020) The most important challenges ahead of microbiome pattern in the post era of the COVID-19 pandemic. J Diabetes Metab Disord:1–3. https://doi.org/10.1007/s40200-020-00579-0

El-Sharkawy AM, Sahota O, Lobo DN (2015) Acute and chronic effects of hydration status on health. Nutr Rev 73(Suppl 2):97–109. https://doi.org/10.1093/nutrit/nuv038

Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, Sabbour M, Gebril S, Nasser M, Kamel M, Amir A, Maher Emara M, Nabhan A (2020) A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet 150(1):47–52. https://doi.org/10.1002/ijgo.13182

Fan J, Li X, Gao Y, Zhou J, Wang S, Huang B, Wu J, Cao Q, Chen Y, Wang Z, Luo D, Zhou T, Li R, Shang Y, Nie X (2020) The lung tissue microbiota features of 20 deceased patients with COVID-19. J Infect 81(3):e64–e67. https://doi.org/10.1016/j.jinf.2020.06.047

Fan Y, Pedersen O (2021) Gut microbiota in human metabolic health and disease. Nat Rev Microbiol 19(1):55–71. https://doi.org/10.1038/s41579-020-0433-9

Feleszko W, Jaworska J, Rha RD, Steinhausen S, Avagyan A, Jaudszus A, Ahrens B, Groneberg DA, Wahn U, Hamelmann E (2007) Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. Clin Exp Allergy 37(4):498–505. https://doi.org/10.1111/j.1365-2222.2006.02629.x

Ferreira C, Viana SD, Reis F (2020) Gut microbiota Dysbiosis-immune Hyperresponse-inflammation triad in coronavirus disease 2019 (COVID-19): impact of pharmacological and nutraceutical approaches. Microorganisms 8(10). https://doi.org/10.3390/microorganisms8101514

Forbes JD, Knox NC, Ronholm J, Pagotto F, Reimer A (2017) Metagenomics: the next culture-independent game changer. Front Microbiol 8:1069. https://doi.org/10.3389/fmicb.2017.01069

Francino MP (2015) Antibiotics and the human gut microbiome: Dysbioses and accumulation of resistances. Front Microbiol 6:1543. https://doi.org/10.3389/fmicb.2015.01543

Frank DN, Feazel LM, Bessesen MT, Price CS, Janoff EN, Pace NR (2010) The human nasal microbiota and Staphylococcus aureus carriage. PLoS One 5(5):e10598. https://doi.org/10.1371/journal.pone.0010598

Frohlich EE, Farzi A, Mayerhofer R, Reichmann F, Jacan A, Wagner B, Zinser E, Bordag N, Magnes C, Frohlich E, Kashofer K, Gorkiewicz G, Holzer P (2016) Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. Brain Behav Immun 56:140–155. https://doi.org/10.1016/j.bbi.2016.02.020

From the American Association of Neurological Surgeons ASoNC, Interventional Radiology Society of Europe CIRACoNSESoMINTESoNESOSfCA, Interventions SoIRSoNS, World Stroke O, Sacks D, Baxter B, BCV C, Carpenter JS, Cognard C, Dippel D, Eesa M, Fischer U, Hausegger K, Hirsch JA, Shazam Hussain M, Jansen O, Jayaraman MV, Khalessi AA, Kluck BW, Lavine S, Meyers PM, Ramee S, Rufenacht DA, Schirmer CM, Vorwerk D (2018) Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. Int J Stroke 13(6):612–632. https://doi.org/10.1177/1747493018778713

Getahun H, Smith I, Trivedi K, Paulin S, Balkhy HH (2020) Tackling antimicrobial resistance in the COVID-19 pandemic. Bull World Health Organ 98(7):442–442A. https://doi.org/10.2471/BLT.20.268573

Gisolfi CV (2000) Is the GI system built for exercise? News Physiol Sci 15:114–119. https://doi.org/10.1152/physiologyonline.2000.15.3.114

Gou W, Fu Y, Yue L, Chen GD, Cai X, Shuai M, Xu F, Yi X, Chen H, Zhu YJ, Xiao ML (2020) Gut microbiota may underlie the predisposition of healthy individuals to COVID-19. MedRxiv. https://doi.org/10.1101/2020.04.22.20076091

Greenwood JM, Ezquerra AL, Behrens S, Branca A, Mallet L (2016) Current analysis of host-parasite interactions with a focus on next generation sequencing data. Zoology (Jena) 119(4):298–306. https://doi.org/10.1016/j.zool.2016.06.010

Han M, Zha Y, Chong H, Zhong C, Ning K (2020) Utilizing microbiome approaches to assist source tracking, treatment and prevention of COVID-19: review and assessment. Comput Struct Biotechnol J 18:3615–3622. https://doi.org/10.1016/j.csbj.2020.11.027

Hiergeist A, Glasner J, Reischl U, Gessner A (2015) Analyses of intestinal microbiota: culture versus sequencing. ILAR J 56(2):228–240. https://doi.org/10.1093/ilar/ilv017

Hikmet F, Mear L, Edvinsson A, Micke P, Uhlen M, Lindskog C (2020) The protein expression profile of ACE2 in human tissues. Mol Syst Biol 16(7):e9610. https://doi.org/10.15252/msb.20209610

Hills RD Jr, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR (2019) Gut microbiome: profound implications for diet and disease. Nutrients 11(7). https://doi.org/10.3390/nu11071613

Hooper LV, Littman DR, Macpherson AJ (2012) Interactions between the microbiota and the immune system. Science 336(6086):1268–1273. https://doi.org/10.1126/science.1223490

Hovhannisyan H, Gabaldon T (2019) Transcriptome sequencing approaches to elucidate host-microbe interactions in opportunistic human fungal pathogens. Curr Top Microbiol Immunol 422:193–235. https://doi.org/10.1007/82_2018_122

Hui AW, Lau HW, Chan TH, Tsui SK (2013) The human microbiota: a new direction in the investigation of thoracic diseases. J Thorac Dis 5(Suppl 2):S127–S131. https://doi.org/10.3978/j.issn.2072-1439.2013.07.41

Ichinohe T, Pang IK, Kumamoto Y, Peaper DR, Ho JH, Murray TS, Iwasaki A (2011) Microbiota regulates immune defense against respiratory tract influenza a virus infection. Proc Natl Acad Sci U S A 108(13):5354–5359. https://doi.org/10.1073/pnas.1019378108

Jiang D, Armour CR, Hu C, Mei M, Tian C, Sharpton TJ, Jiang Y (2019) Microbiome multi-Omics network analysis: statistical considerations, limitations, and opportunities. Front Genet 10:995. https://doi.org/10.3389/fgene.2019.00995

Johnson AJ, Zheng JJ, Kang JW, Saboe A, Knights D, Zivkovic AM (2020) A guide to diet-microbiome study design. Front Nutr 7:79. https://doi.org/10.3389/fnut.2020.00079

Keim NL, Martin RJ (2014) Dietary whole grain-microbiota interactions: insights into mechanisms for human health. Adv Nutr 5(5):556–557. https://doi.org/10.3945/an.114.006536

Kesh K, Mendez R, Abdelrahman L, Banerjee S, Banerjee S (2020) Type 2 diabetes induced microbiome dysbiosis is associated with therapy resistance in pancreatic adenocarcinoma. Microb Cell Factories 19(1):75. https://doi.org/10.1186/s12934-020-01330-3

Khatiwada S, Subedi A (2020) Lung microbiome and coronavirus disease 2019 (COVID-19): possible link and implications. Hum Microb J 17:100073. https://doi.org/10.1016/j.humic.2020.100073

Kim S, Covington A, Pamer EG (2017) The intestinal microbiota: antibiotics, colonization resistance, and enteric pathogens. Immunol Rev 279(1):90–105. https://doi.org/10.1111/imr.12563

Kirby TO, Ochoa-Reparaz J (2018) The gut microbiome in multiple sclerosis: a potential therapeutic avenue. Med Sci (Basel) 6(3). https://doi.org/10.3390/medsci6030069

Konstantinidis T, Tsigalou C, Karvelas A, Stavropoulou E, Voidarou C, Bezirtzoglou E (2020) Effects of antibiotics upon the gut microbiome: a review of the literature. Biomedicine 8(11). https://doi.org/10.3390/biomedicines8110502

Kyle MH, Glassman ME, Khan A, Fernandez CR, Hanft E, Emeruwa UN, Scripps T, Walzer L, Liao GV, Saslaw M, Rubenstein D, Hirsch DS, Keown MK, Stephens A, Mollicone I, Bence ML, Gupta A, Sultan S, Sibblies C, Whittier S, Abreu W, Akita F, Penn A, Orange JS, Saiman L, Welch MG, Gyamfi-Bannerman C, Stockwell MS, Dumitriu D (2020) A review of newborn outcomes during the COVID-19 pandemic. Semin Perinatol 44(7):151286. https://doi.org/10.1016/j.semperi.2020.151286

Langevin S, Pichon M, Smith E, Morrison J, Bent Z, Green R, Barker K, Solberg O, Gillet Y, Javouhey E, Lina B, Katze MG, Josset L (2017) Early nasopharyngeal microbial signature associated with severe influenza in children: a retrospective pilot study. J Gen Virol 98(10):2425–2437. https://doi.org/10.1099/jgv.0.000920

Lau K, Srivatsav V, Rizwan A, Nashed A, Liu R, Shen R, Akhtar M (2017) Bridging the gap between gut microbial Dysbiosis and cardiovascular diseases. Nutrients 9(8). https://doi.org/10.3390/nu9080859

Lebeer S, Spacova I (2019) Exploring human host-microbiome interactions in health and disease-how to not get lost in translation. Genome Biol 20(1):56. https://doi.org/10.1186/s13059-019-1669-4

Lee SR (2018) Critical role of zinc as either an antioxidant or a Prooxidant in cellular systems. Oxidative Med Cell Longev 2018:9156285. https://doi.org/10.1155/2018/9156285

Lee SY, Lee E, Park YM, Hong SJ (2018) Microbiome in the gut-skin Axis in atopic dermatitis. Allergy Asthma Immunol Res 10(4):354–362. https://doi.org/10.4168/aair.2018.10.4.354

Lee YB, Byun EJ, Kim HS (2019) Potential role of the microbiome in acne: a comprehensive review. J Clin Med 8(7). https://doi.org/10.3390/jcm8070987

Leis JA, Born KB, Theriault G, Ostrow O, Grill A, Johnston KB (2020) Using antibiotics wisely for respiratory tract infection in the era of covid-19. BMJ 371:m4125. https://doi.org/10.1136/bmj.m4125

Lemon KP, Klepac-Ceraj V, Schiffer HK, Brodie EL, Lynch SV, Kolter R (2010) Comparative analyses of the bacterial microbiota of the human nostril and oropharynx. mBio 1(3). https://doi.org/10.1128/mBio.00129-10

Lim S, Bae JH, Kwon HS, Nauck MA (2021) COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 17(1):11–30. https://doi.org/10.1038/s41574-020-00435-4

Ling Z, Liu X, Luo Y, Yuan L, Nelson KE, Wang Y, Xiang C, Li L (2013) Pyrosequencing analysis of the human microbiota of healthy Chinese undergraduates. BMC Genomics 14:390. https://doi.org/10.1186/1471-2164-14-390

Magana M, Pushpanathan M, Santos AL, Leanse L, Fernandez M, Ioannidis A, Giulianotti MA, Apidianakis Y, Bradfute S, Ferguson AL, Cherkasov A, Seleem MN, Pinilla C, de la Fuente-Nunez C, Lazaridis T, Dai T, Houghten RA, Hancock REW, Tegos GP (2020) The value of antimicrobial peptides in the age of resistance. Lancet Infect Dis 20(9):e216–e230. https://doi.org/10.1016/S1473-3099(20)30327-3

Maleki Dana P, Kolahdooz F, Sadoughi F, Moazzami B, Chaichian S, Asemi Z (2020) COVID-19 and pregnancy: a review of current knowledge. Infez Med 28(suppl 1):46–51

Malinis M, McManus D, Davis M, Topal J (2020) An overview on the use of antivirals for the treatment of patients with COVID19 disease. Expert Opin Investig Drugs:1–15. https://doi.org/10.1080/13543784.2021.1847270

Malla MA, Dubey A, Kumar A, Yadav S, Hashem A, Abd Allah EF (2018) Exploring the human microbiome: the potential future role of next-generation sequencing in disease diagnosis and treatment. Front Immunol 9:2868. https://doi.org/10.3389/fimmu.2018.02868

Mansur JL (2020) Letter: low population mortality from COVID-19 in countries south of latitude 35 degrees north supports vitamin D as a factor determining severity. Aliment Pharmacol Ther 52(2):411–412. https://doi.org/10.1111/apt.15820

McCartney DM, Byrne DG (2020) Optimisation of vitamin D status for enhanced Immunoprotection against Covid-19. Ir Med J 113(4):58

McCullers JA, Rehg JE (2002) Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 186(3):341–350. https://doi.org/10.1086/341462

Morais LH, HLT S, Mazmanian SK (2020) The gut microbiota-brain axis in behaviour and brain disorders. Nat Rev Microbiol. https://doi.org/10.1038/s41579-020-00460-0

Morris A, Beck JM, Schloss PD, Campbell TB, Crothers K, Curtis JL, Flores SC, Fontenot AP, Ghedin E, Huang L, Jablonski K, Kleerup E, Lynch SV, Sodergren E, Twigg H, Young VB, Bassis CM, Venkataraman A, Schmidt TM, Weinstock GM, Lung HIVMP (2013) Comparison of the respiratory microbiome in healthy nonsmokers and smokers. Am J Respir Crit Care Med 187(10):1067–1075. https://doi.org/10.1164/rccm.201210-1913OC

Neu J, Rushing J (2011) Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol 38(2):321–331. https://doi.org/10.1016/j.clp.2011.03.008

Neuman H, Forsythe P, Uzan A, Avni O, Koren O (2018) Antibiotics in early life: dysbiosis and the damage done. FEMS Microbiol Rev 42(4):489–499. https://doi.org/10.1093/femsre/fuy018

Nuriel-Ohayon M, Neuman H, Koren O (2016) Microbial changes during pregnancy, birth, and infancy. Front Microbiol 7:1031. https://doi.org/10.3389/fmicb.2016.01031

O'Hara AM, Shanahan F (2006) The gut flora as a forgotten organ. EMBO Rep 7(7):688–693. https://doi.org/10.1038/sj.embor.7400731

Olaimat AN, Aolymat I, Al-Holy M, Ayyash M, Abu Ghoush M, Al-Nabulsi AA, Osaili T, Apostolopoulos V, Liu SQ, Shah NP (2020) The potential application of probiotics and prebiotics for the prevention and treatment of COVID-19. NPJ Sci Food 4:17. https://doi.org/10.1038/s41538-020-00078-9

Pascal M, Perez-Gordo M, Caballero T, Escribese MM, Lopez Longo MN, Luengo O, Manso L, Matheu V, Seoane E, Zamorano M, Labrador M, Mayorga C (2018) Microbiome and allergic diseases. Front Immunol 9:1584. https://doi.org/10.3389/fimmu.2018.01584

Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, Scarlata S, Agro FE (2020) COVID-19 diagnosis and management: a comprehensive review. J Intern Med 288(2):192–206. https://doi.org/10.1111/joim.13091

Peters HP, De Vries WR, Vanberge-Henegouwen GP, Akkermans LM (2001) Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. Gut 48(3):435–439. https://doi.org/10.1136/gut.48.3.435

Picca A, Fanelli F, Calvani R, Mule G, Pesce V, Sisto A, Pantanelli C, Bernabei R, Landi F, Marzetti E (2018) Gut Dysbiosis and muscle aging: searching for novel targets against sarcopenia. Mediat Inflamm 2018:7026198. https://doi.org/10.1155/2018/7026198

Pulikkan J, Maji A, Dhakan DB, Saxena R, Mohan B, Anto MM, Agarwal N, Grace T, Sharma VK (2018) Gut microbial Dysbiosis in Indian children with autism Spectrum disorders. Microb Ecol 76(4):1102–1114. https://doi.org/10.1007/s00248-018-1176-2

Quigley EM (2013) Gut bacteria in health and disease. Gastroenterol Hepatol (N Y) 9(9):560–569

Rajkumar RP (2020) COVID-19 and mental health: a review of the existing literature. Asian J Psychiatr 52:102066. https://doi.org/10.1016/j.ajp.2020.102066

Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G (2019) The role of zinc in antiviral immunity. Adv Nutr 10(4):696–710. https://doi.org/10.1093/advances/nmz013

Riccio P, Rossano R (2018) Diet, gut microbiota, and vitamins D + a in multiple sclerosis. Neurotherapeutics 15(1):75–91. https://doi.org/10.1007/s13311-017-0581-4

Rishi P, Thakur K, Vij S, Rishi L, Singh A, Kaur IP, Patel SKS, Lee JK, Kalia VC (2020) Diet, gut microbiota and COVID-19. Indian J Microbiol:1–10. https://doi.org/10.1007/s12088-020-00908-0

Rodgers GP, Gibbons GH (2020) Obesity and hypertension in the time of COVID-19. JAMA 324(12):1163–1165. https://doi.org/10.1001/jama.2020.16753

Roy D, Tripathy S, Kar SK, Sharma N, Verma SK, Kaushal V (2020) Study of knowledge, attitude, anxiety & perceived mental healthcare need in Indian population during COVID-19 pandemic. Asian J Psychiatr 51:102083. https://doi.org/10.1016/j.ajp.2020.102083

Sadiq FA (2021) Is it time for microbiome-based therapies in viral infections? Virus Res 291:198203. https://doi.org/10.1016/j.virusres.2020.198203

Saffouri GB, Shields-Cutler RR, Chen J, Yang Y, Lekatz HR, Hale VL, Cho JM, Battaglioli EJ, Bhattarai Y, Thompson KJ, Kalari KK, Behera G, Berry JC, Peters SA, Patel R, Schuetz AN, Faith JJ, Camilleri M, Sonnenburg JL, Farrugia G, Swann JR, Grover M, Knights D, Kashyap PC (2019) Small intestinal microbial dysbiosis underlies symptoms associated with functional gastrointestinal disorders. Nat Commun 10(1):2012. https://doi.org/10.1038/s41467-019-09964-7

Sattar N, McInnes IB, McMurray JJV (2020) Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation 142(1):4–6. https://doi.org/10.1161/CIRCULATIONAHA.120.047659

Segal LN, Alekseyenko AV, Clemente JC, Kulkarni R, Wu B, Gao Z, Chen H, Berger KI, Goldring RM, Rom WN, Blaser MJ, Weiden MD (2013) Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. Microbiome 1(1):19. https://doi.org/10.1186/2049-2618-1-19

Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S (2020) Overview of immune response during SARS-CoV-2 infection: lessons from the past. Front Immunol 11:1949. https://doi.org/10.3389/fimmu.2020.01949

Sheflin AM, Whitney AK, Weir TL (2014) Cancer-promoting effects of microbial dysbiosis. Curr Oncol Rep 16(10):406. https://doi.org/10.1007/s11912-014-0406-0

Shen Z, Xiao Y, Kang L, Ma W, Shi L, Zhang L, Zhou Z, Yang J, Zhong J, Yang D, Guo L, Zhang G, Li H, Xu Y, Chen M, Gao Z, Wang J, Ren L, Li M (2020) Genomic diversity of severe acute respiratory syndrome-coronavirus 2 in patients with coronavirus disease 2019. Clin Infect Dis 71(15):713–720. https://doi.org/10.1093/cid/ciaa203

Shi Y, Wang G, Cai XP, Deng JW, Zheng L, Zhu HH, Zheng M, Yang B, Chen Z (2020) An overview of COVID-19. J Zhejiang Univ Sci B 21(5):343–360. https://doi.org/10.1631/jzus.B2000083

Shinu P, Morsy MA, Deb PK, Nair AB, Goyal M, Shah J, Kotta S (2020) SARS CoV-2 organotropism associated pathogenic relationship of gut-brain Axis and illness. Front Mol Biosci 7:606779. https://doi.org/10.3389/fmolb.2020.606779

Short KR, Habets MN, Hermans PW, Diavatopoulos DA (2012) Interactions between Streptococcus pneumoniae and influenza virus: a mutually beneficial relationship? Future Microbiol 7(5):609–624. https://doi.org/10.2217/fmb.12.29

Swiatecka D, Narbad A, Ridgway KP, Kostyra H (2011) The study on the impact of glycated pea proteins on human intestinal bacteria. Int J Food Microbiol 145(1):267–272. https://doi.org/10.1016/j.ijfoodmicro.2011.01.002

Thursby E, Juge N (2017) Introduction to the human gut microbiota. Biochem J 474(11):1823–1836. https://doi.org/10.1042/BCJ20160510

Vangay P, Ward T, Gerber JS, Knights D (2015) Antibiotics, pediatric dysbiosis, and disease. Cell Host Microbe 17(5):553–564. https://doi.org/10.1016/j.chom.2015.04.006

Varghese PM, Tsolaki AG, Yasmin H, Shastri A, Ferluga J, Vatish M, Madan T, Kishore U (2020) Host-pathogen interaction in COVID-19: pathogenesis, potential therapeutics and vaccination strategies. Immunobiology 225(6):152008. https://doi.org/10.1016/j.imbio.2020.152008

Venkataraman A, Bassis CM, Beck JM, Young VB, Curtis JL, Huffnagle GB, Schmidt TM (2015) Application of a neutral community model to assess structuring of the human lung microbiome. mBio 6(1). https://doi.org/10.1128/mBio.02284-14

Villapol S (2020) Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res 226:57–69. https://doi.org/10.1016/j.trsl.2020.08.004

West CE, Dzidic M, Prescott SL, Jenmalm MC (2017) Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention. Allergol Int 66(4):529–538. https://doi.org/10.1016/j.alit.2017.08.001

Yang I, Corwin EJ, Brennan PA, Jordan S, Murphy JR, Dunlop A (2016) The infant microbiome: implications for infant health and neurocognitive development. Nurs Res 65(1):76–88. https://doi.org/10.1097/NNR.0000000000000133

Yang R, Mei H, Zheng T, Fu Q, Zhang Y, Buka S, Yao X, Tang Z, Zhang X, Qiu L, Zhang Y, Zhou J, Cao J, Wang Y, Zhou A (2020) Pregnant women with COVID-19 and risk of adverse birth outcomes and maternal-fetal vertical transmission: a population-based cohort study in Wuhan. China BMC Med 18(1):330. https://doi.org/10.1186/s12916-020-01798-1

Yang YJ, Sheu BS (2012) Probiotics-containing yogurts suppress helicobacter pylori load and modify immune response and intestinal microbiota in the helicobacter pylori-infected children. Helicobacter 17(4):297–304. https://doi.org/10.1111/j.1523-5378.2012.00941.x

Yi H, Yong D, Lee K, Cho YJ, Chun J (2014) Profiling bacterial community in upper respiratory tracts. BMC Infect Dis 14:583. https://doi.org/10.1186/s12879-014-0583-3

Young VB (2017) The role of the microbiome in human health and disease: an introduction for clinicians. BMJ 356:j831. https://doi.org/10.1136/bmj.j831

Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, Woodworth KR, Nahabedian JF 3rd, Azziz-Baumgartner E, Gilboa SM, Meaney-Delman D (2020) Pregnancy CC-R, infant linked outcomes T (2020) update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status–United States, January 22-October 3. MMWR Morb Mortal Wkly Rep 69(44):1641–1647. https://doi.org/10.15585/mmwr.mm6944e3

Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung ACK, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC (2020) Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 159(3):944–955. e948. https://doi.org/10.1053/j.gastro.2020.05.048