

BIODIVERSITY, HUMAN MICROBIOME AND INFECTIOUS DISEASES

Elisa Biliotti

*Istituto Nazionale Malattie Infettive (INMI) 'Lazzaro Spallanzani' IRCCS– Roma, Italy.

Abstract

Infectious diseases have long posed an important threat to global health, causing significant morbidity and mortality worldwide and requiring constant innovation in treatment approaches. The perception of microbes has considerably changed since the recognition of their pathogenic potential in the 19th century. Recent research has shed light on the role of human microbiome, its interplay with animal and environmental microbiomes and dysbiosis in determining the susceptibility, severity, and outcome of infectious diseases. This article addresses the intricate relationship between the microbiome and infectious diseases, highlighting how biodiversity loss can impact microbial balance and human health. It reveals the role of microbiome as a crucial mediator of host-pathogen interactions and explore the remarkable potential of modulating this dynamic ecosystem to develop innovative personalised treatment strategies that could optimize the management of infectious diseases.

Keywords

Biodiversity, human microbiome, infectious diseases, dysbiosis

1. Introduction

The human body is inhabited by a multitude of microorganisms (bacteria, viruses, fungi, archaea) that collectively form the microbiota. Microbiota, the genetic materials and metabolites, the specific environment occupied constitute the microbiome. In humans, the intestine hosts the greatest number of microorganisms and the greatest variety of species (intestinal microbiome) compared to other parts of the body, followed by the skin, respiratory tract, mouth, urinary tract and reproductive organs.

A strict relationship between microbiome, human health and disease has been demonstrated for a long time. Maintaining a high level of biodiversity within the human microbiome is considered crucial for host health and resistance against pathogens.

In the last decade, the impact of microbiome on infectious disease raised a great interest among researchers, since the host, the infectious agent, and the environment are three main factors in the pathogenesis and development of infectious diseases (Biliotti, 2024).

The objectives of this article are to explore the current knowledge about the role of the human microbiome in the susceptibility, pathogenesis and outcome of certain major infectious diseases and

to highlight potential treatment strategies that target the microbiome.

2. Infectious Diseases

Infectious diseases remain a major global health challenge, causing significant morbidity and mortality worldwide. In the late 19th century, physicians and microbiologists began to divide the microbes with which humans were in contact into two categories: pathogens (microbes causing infections) and all the others, termed commensals (Haraoui, 2023). For decades, the study of infectious diseases has focused primarily on pathogens, as central to the aetiopathogenesis of infectious diseases. This schema for infectious diseases was originally postulated by Robert Koch, according to his theory, infection occurs in a linear progression: a pathogen microorganism enters the host, colonizes and causes disease (Koch, 1876; Grimes, 2006). Therefore, for over a century, research has focused on the mechanisms by which a pathogen can overcome host defences and establish infection. Recently, researchers extended their attention from a focus on the host–pathogen interaction to how the indigenous microbiome is an additional element that plays a critical role in determining susceptibility to, and outcomes of, infectious diseases.

3. Microbiome and Biodiversity

Humans and other living organisms as well as ecosystems host a vast community of microorganisms, termed the microbiome. In humans, the microbiome, acquired at birth from the mother, changes during the first years of life, until it reaches stability towards the age of 5 years.

Normal microbiome content is determined by environment, lifestyle factors, diet, socioeconomic status, social and political context.

Traditionally, humans and their microbiomes have been studied separately from the other domains that surround them. However, it is now clear that substantial strain-sharing occurs between humans, between humans and animals, as well as with the environment.

The strain-sharing between humans and animals seem to be directly related to the intensity of their contacts, as shown in adult dog owners, whose skin microbiota is comparable to their own dogs, with a significant increase in bacterial diversity observed on their hands. The strain-sharing between humans and animals also includes antimicrobial resistance strains, as shown in chicken farmers, who share resistant strains with their poultry.

Lastly, there is also extensive sharing between the environment and animals, including humans. This occurs through food, tap water or close contact with nature, which leads to overall and long-lasting changes in the intestinal and skin human microbiomes.

Likewise, animals and humans can also directly spread strains to the environment, such as through excrement dispersion into soils, water or air. This stresses the importance of ecosystem health to maintain biodiversity, a healthy microbiome and ultimately our own health (Muhummed, 2025).

4. Dysbiosis and Infectious Diseases

A human healthy microbiome is the most important mechanism of defence against infections, since its main function is the ability of beneficial microbes to prevent harmful ones from establishing infection.

The main mechanisms of protection against infectious pathogens are three, the first is competition for nutrients and space, the second is production of antimicrobial compounds and the third is stimulation of host immunity.

The imbalance or disruption in the composition and function of the microbiome leads to dysbiosis, that cause compromised host immune response and increased susceptibility to infection and development of infectious diseases (Carding, 2015; Libertucci, 2019).

5. Microbiome and Respiratory Infections

Lung microbiome is composed by diverse and dynamic microbial communities, which live in the upper (nasal, mouth, trachea, upper bronchus) and lower (lungs, bronchi, bronchioles, and alveoli) mucosal area of the respiratory tract. The respiratory microbiome exists along a gradient, with microbial diversity highest in the upper respiratory tract and decreasing towards the lower respiratory tract. The healthy upper airway microbiome is dominated by *Streptococci*, *Neisseria*, *Prevotella*, *Rothia* and *Haemophilus*. The lower respiratory tract has significantly reduced bacterial concentration and differing diversity compared with the upper airway. The microbiome is characterised by *Bacteroidetes*, *Proteobacteria*, *Firmicutes*, followed by lesser proportions of *Actinobacteria*.

Lung microbiome is transient, change over time and is influenced by the external environment and adjacent body parts, since it is strongly related to the oropharyngeal and gut microbiomes.

Oropharyngeal microbiome has an impact on the production, maintenance, and changes in the pulmonary microbial community, as a consequence, oral health has been shown to be associated with the risk of developing respiratory diseases.

The gut microbiome influences the lung microbiome (gut-lung axis) by producing ligands, metabolites, and immune cells that reach the lungs via the bloodstream to regulate innate and adaptative pulmonary immunity.

The change in the status of the pulmonary microbiome from eubiosis to dysbiosis can reduce the respiratory mechanisms of defence, making individuals more susceptible to pathogen colonization and infection, such as pneumonia, coronavirus disease-19 (COVID-19) and tuberculosis (Moffatt, 2017).

Pneumonia is an inflammatory condition of the lungs usually caused by bacteria, viruses, or fungi, which are responsible of a heterogeneous cluster of illnesses that encompasses community acquired

pneumonia (CAP), healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Microorganisms that represent the normal flora of the upper respiratory tract and co-exist with other microorganisms can become pathogenic if the host immunity is compromised and the normal equilibrium is disturbed. This can lead to the over growth of the pathogenic organism and dissemination to the lower respiratory tract leading to pneumonia (Narendrakumar & Ray, 2022).

A lot of studies demonstrate that orotracheal intubation impairs the natural lung immune system and cause important changes in both oropharyngeal and lung microbiome, in fact, there is a significant decrease in the diversity and in the species of microbes detected in the endotracheal aspirate in VAP patients compared to that of patients who have no VAP but are intubated (Zakharkina T Thorax 2017; Woo S J Clin Med 2020).

Therefore, among the strategies identified to reduce VAP incidence, providing good oral hygiene to patients who are on mechanical ventilation is an important strategy to lower the incidence of VAP in mechanically ventilated patients.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can be associated with gastrointestinal symptoms. Recent studies suggest that SARS-CoV-2 is able to cause gut dysbiosis, since a reduction in bacterial diversity and an increase in the presence of opportunistic pathogens, including *Streptococcus*, *Rothia*, *Veillonella*, *Erysipelatoclostridium*, and *Actinomyces*, has been observed in subjects affected by COVID-19 (Zuo et al., 2020; Alves et al., 2025).

In the context of SARS-CoV-2 infection, a balanced gut microbiome is crucial for an efficient immune response, preventing excessive reactions that could compromise vital organs such as the lungs. In fact, the main pathogenic mechanism of SARS-CoV-2 consists of triggering host exacerbated immune responses, known as cytokine storms, the intensity of which seems to be modulated by the gut microbiota. Factors such as aging, diet, comorbidities (obesity, diabetes, cardiovascular diseases) play a crucial role in microbiota composition, exacerbating both dysbiosis and systemic inflammation and potentially influencing COVID-19 severity (Alves et al., 2025). In addition to the gut microbiota,

alterations of oral microbiota composition have been observed in SARS-CoV-2 infected patients, which may serve as an additional source of endotoxins, contributing to the amplification of systemic inflammation observed in more severe cases of COVID-19 (Ren, 2021). The prolonged effects of SARS-CoV-2 on the microbiota have been demonstrated by the persistence of intestinal dysbiosis even after recovery from infection. In this context, emerging evidence suggest a significant role of the microbiome in the establishment of viral reservoirs and in the pathogenesis of long COVID. Persistent viral presence in tissues may trigger ongoing immune activation and inflammation, contributing to prolonged symptoms (Proal et al., 2023). Alterations in the gut-brain axis have been associated with central nervous system chronic inflammation and neuropsychiatric symptoms seen in long COVID cases (Zollner et al., 2024).

Tuberculosis is an infectious disease caused by the alcohol-acid-resistant bacillus *Mycobacterium tuberculosis*. It is a highly transmissible infection spread by aerosol droplets containing bacilli, usually during sneezing or coughing (Eribo et al., 2020). In most individuals the infection results in clinically asymptomatic latent tuberculosis infection, but 5-10% of cases develop tuberculosis that generally involves the lungs. Beside host immunity, genetic and environmental factors, the gut and the lung microbiome seem to play a critical role in regulating host immunity and contributing to tuberculosis pathogenesis (Maciel-Fiuza et al., 2023).

Studies have shown remarkable differences between the gut and lung microbiome of patients affected by tuberculosis and healthy-controls, intestinal and lung microbiome diversity is decreased in patients with pulmonary tuberculosis.

Specifically, depletion of short-chain fatty acids (SCFAs) producing genera, which are critical for maintaining immune homeostasis through butyrate-mediated macrophage regulation, impairs macrophage bactericidal activity affecting disease's onset, progression, and prognosis.

In addition, the reduction of *Lactobacilli* and *Bifidobacteria* cause an impairment of gut barrier function leading to an increase of gut permeability.

This impairment allows pathogens and inflammatory mediators to enter the bloodstream more easily and trigger systemic inflammation,

which is a key factor of the pathogenesis of tuberculosis and its progression (Chai et al., 2025).

Human microbiome has become a crucial area of research in the field of respiratory infections. An accurate investigation of the mechanisms by it participates in the susceptibility, pathogenesis and immunomodulation of respiratory infections could lead to the development of novel therapeutic strategies and innovative approaches to disease management.

6. *Microbiome and Urinary Tract Infections (UTIs)*

Urinary tract infections (UTIs) are among the most common bacterial infections worldwide and encompass a broad spectrum of diseases, ranging from uncomplicated cystitis to life-threatening urosepsis. The urinary tract hosts a rich and complex microbial community, the urobiome. The urinary tract microbiome composition appears to play an important role in urinary tract defense, and its disequilibrium may contribute to infection as much as the invading uro-pathogen itself.

In addition, interactions between different microbial communities, such as the gut and vagina, are also major contributors to UTIs. Most UTIs result from periurethral contamination originating from gut microbiota.

Intestinal proliferation of uro-pathogenic bacteria followed by subsequent colonization of the bladder is one of the proposed mechanisms underlying recurrent UTIs (Flores-Mireles et al., 2015). Higher relative abundances of *Escherichia* and *Enterococcus* in the gut were independently associated with subsequent development of bacteriuria and UTIs caused by these organisms, demonstrating the relevance of the gut-urinary tract microbiota axis (Magruder et al., 2019).

Recent studies demonstrate that faecal microbiota transplantation (FMT) may reduce recurrent UTIs for the following suggested reasons.

First, FMT restores colonization by reintroducing a diverse and balanced microbial community that competes with uropathogens, limiting their overgrowth and translocation.

Second, FMT modulates immune and inflammatory responses through increased abundance of beneficial taxa producing short chain fatty acids, which enhance mucosal barrier integrity and host defence.

Third, shifts in microbial metabolic and signalling pathways following FMT may suppress virulence factors and biofilm formation in potential pathogens.

It has also been suggested that vaginal microbiota transplantation might be useful for recurrent UTIs (Belvončíková & Gardlik, 2025).

7. *Microbiome and Clostridioides Difficile Infections (CDI)*

Clostridium difficile (CD) is a Gram-positive, spore-forming bacterium which grows in obligate anaerobic conditions and is a member of the normal gut microbiota. CD relies on the formation of spores for survival and transmission outside of the anaerobic gut environment, spores are metabolically dormant until encountering appropriate environmental cues in the gut that induce germination. For CD, this process is driven by primary bile acids produced by the host in the liver and released into the gastrointestinal tract.

Colonization resistance to CD is maintained by the gut microbiota, which occupies space in the gut and transforms bile acids from the colon into secondary bile acids (Ridlon, 2024; McMillan, & Theriot, 2024).

Disruption of the gut microbiota by diminishing a large portion of bacterial taxa, such as following antibiotic use, removes these functions, leaving a metabolic environment amenable for CD spore germination and outgrowth.

Upon germination into metabolically active vegetative cells, CD produces the major disease-causing toxins, toxin A and toxin B. CD toxins mount a potent assault on intestinal epithelial, immune, neuronal cells and cause barrier breakdown and propagation of systemic disease, causing a wide range of clinical symptoms, from mild to moderate or severe diarrhoea to toxic megacolon.

Ultimately, CD forms resilient spores, which ensures long-term persistence within the host, poised to reinitiate the pathogenic cycle whenever favourable conditions present itself (recurrent CDI). Effective treatment and prevention of CDI require a therapeutic strategy that addresses three core criteria: the first, prevention of initial colonization; the second, treatment of the disease and mitigation of toxin-mediated tissue damage; the third, inhibition of spore dissemination and persistence.

The prevention of initial colonization requires a multimodal approach, including hand hygiene with soap and water, contact precautions, environmental decontamination with sporicidal cleaning agents, minimizing or avoiding unnecessary antibiotic exposure (or selecting the lowest-risk effective antibiotic when necessary), routine use of auditing and feedback to ensure effectiveness of all infection prevention, infection control, and stewardship measures (Vence & Turner, 2025).

Treatment of primary and recurrent CDI consist of a course of antibiotics (vancomycin, fidaxomicin), that is largely effective at killing vegetative CD cells, but has no effect on spores.

More recent therapies such as monoclonal antibody or pharmacologic agents targeting toxin A and toxin B inhibit toxin activity, thus preventing tissue damage (Wilcox, 2017).

The main limitation of these therapies is that are able to limit clinical symptoms of disease, but they do not address microbiota disruption or spore persistence, leading to recurrent CDI in approximately 25% of patients after initial treatment.

FMT or next-generation microbiome-based therapies offer another promising route to restore microbial homeostasis and prevent colonization, potentially disrupting the pathogenic cycle at its origin (Seekatz, 2025).

8. Microbiome and Human Papilloma Virus (HPV) Infections

The microbiome in the female genital tract is an intricate assembly of diverse aerobic, anaerobic, and microaerophilic microorganisms, which share the space within the reproductive tract and engage in complex interactions. The cervicovaginal dominant lactobacilli have been shown to maintain homeostasis through a multitude of mechanisms, including producing antimicrobial substances and competitive exclusion of incursive pathogens, thereby establishing a mutually beneficial relationship with the host. Microbiome dysbiosis, characterized by reduced *Lactobacillus* and increased harmful bacteria like *Gardnerella* and *Prevotella*, may disrupt the symbiotic relationship between the host and microorganisms and play a pivotal role in the pathogenesis of various diseases, including its involvement in the establishment of human papillomavirus (HPV) infection and the

development of associated cervical cancer (CC) (Laniewski et al, 2020). Persistent infection with high-risk human papillomavirus (HR-HPV), particularly types 16 and 18, is recognized as the primary etiological driver of cervical carcinogenesis. The vaginal microbiome affects CC development through modulating genital inflammation and immune responses, influencing HR-HPV oncogene expression and oncoprotein production, regulating oxidative stress and DNA damage and inducing metabolic changes in the tumor microenvironment. Given the main role of the vaginal microbiota in modulating HPV persistence, local immunity, and epithelial integrity, strategies that target microbial dysbiosis are emerging as promising adjuncts to conventional therapies in HPV-associated CC. The microbiome-modulating approaches include the use of probiotics, prebiotics, probiotic-based HPV vaccines and vaginal microbiota transplantation. These therapeutic strategies show promising results in clearing HR-HPV infections, improving cytological abnormalities, and potentially preventing CC progression (Huang, 2024).

9. Conclusions

In summary, the human microbiome constitutes a dynamic and evolving ecosystem characterized by a strict relationship with animal and environment microbiomes. It is considered an actively functioning "organ" that reflects and influences individual's health and disease.

Maintaining and understanding this delicate balance requires a holistic view that considers the impact of environmental biodiversity on human microbial health.

The human microbiome plays a central role in susceptibility, pathogenesis and treatment of infectious diseases, such as pneumonia, COVID-19, tuberculosis, gastrointestinal infections, urinary tract infections and HPV infections.

In this context, therapeutic strategies aimed at modulating the human microbiome, such as the use of probiotics, prebiotics, fiber-rich diets or FMT, emerge as a promising approach to modulate disease severity and to treat infectious diseases.

Future research should prioritize the investigation of advanced and integrative strategies for human microbiome modulation and diagnostic refinement.

This includes the identification of predictive microbial signatures linked to disease severity,

therapeutic responsiveness, and long-term complications, as well as the development of personalized microbiome-based interventions, specifically designed to correct dysbiosis profiles identified in different infectious diseases.

These approaches hold potential to advance precision medicine not only in the context of infectious diseases.

REFERENCES

- Alves, M. C. S., Rego, M. S., Cabral da Silva, M. C., et al. (2025). Gut Microbiota and COVID-19: Unraveling the Gut-Lung Axis and Immunomodulatory Therapies. *ACS Infectious Diseases*, 11(7), 1844–1853.
- Belvončíkova, P., & Gardlik, L. (2025). Faecal microbiota transplantation for urinary tract infections. *Clinical Microbiology and Infection*.
- Biliotti, E. (2024). Biodiversity and Human Microbiota in Health and Disease. *SCIRES-IT - SCientific REsearch and Information Technology*, 14(Special Issue), 25–30. <http://dx.doi.org/10.2423/i22394303v14Sp25>
- Carding, S., Verbeke, K., Vipond, D. T., et al. (2015). Dysbiosis of the gut microbiota in disease. *Microbial Ecology in Health and Disease*, 26, 26191.
- Chai, Y., Li, M., Deng, X., et al. (2025). Gut microbiota and tuberculosis infection: interaction and therapeutic potential. *Gut Microbes*, 17(1).
- Eribo, O. A., Mumin, P., Guler, R., et al. (2020). The gut microbiome in tuberculosis susceptibility and treatment response: guilty or not guilty? *Cellular and Molecular Life Sciences*, 77, 1497–1509.
- Flores-Mireles, A. L., Walker, J. N., Caparon, M., & Hultgren, S. J. (2015). Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nature Reviews Microbiology*, 13, 269–284.
- Grimes, D.J. (2006). Koch's postulates—then and now. *Microbe Magazine*, 1(5), 223–228.
- Haraoui, L.P., & Blaser, M.J. (2023). The Microbiome and Infectious Diseases. *Clinical Infectious Diseases*, 77, S441–S446.
- Huang, R., Liu, Z., Sun, T., et al. (2024). Cervicovaginal microbiome, high-risk HPV infection and cervical cancer: Mechanisms and therapeutic potential. *Microbiological Research*, 287, 127857.
- Koch, R. (1876). Die Ätiologie der milzbrand-krankheit, begründet auf die entwicklungsgeschichte des Bacillus anthracis. *Cohns Beitr. Biol. Pflanzen* 2, 277–310.
- Łaniewski, P., İlhan, Z. E., & Herbst-Kralovetz, M. M. (2020). The microbiome and gynaecological cancer development, prevention and therapy. *Nature Reviews Urology*, 17(4), 232–250.
- Libertucci, J., & Young, V.B. (2019). The role of the microbiota in infectious diseases. *Nature Microbiology*, 4(1), 35–45. <https://doi.org/10.1038/s41564-018-0278-4>
- Maciel-Fiuza, M. F., Muller, G. C., Campos, D. M. S., et al. (2023). Role of gut microbiota in infectious and inflammatory diseases. *Frontiers in Microbiology*, 14, 1098386.
- Magruder, M., Sholi, A. N., Gong, C., Zhang, L., Edusei, E., Huang, J., et al. (2019). Gut uropathogen abundance is a risk factor for development of bacteriuria and urinary tract infection. *Nature Communications*, 10, 5521.
- McMillan, A. S., & Theriot, C. M. (2024). Bile acids impact the microbiota, host, and *C. difficile* dynamics providing insight into mechanisms of efficacy of FMTs and microbiota-focused therapeutics. *Gut Microbes*, 16(1), 2393766.
- Moffatt, M. F., & Cookson, W.O. (2017) The lung microbiome in health and disease. *Clinical Medicine*, 17(6), 525–529. <https://doi.org/10.7861/clinmedicine.17-6-525>

- Muhummed, A. M., Lanker, K. C., Yersin, S., & Zinsstag, J. (2025). One Health, One Microbiome. *Microbiome*, 13(1), 216. <https://doi.org/10.1186/s40168-025-02231-6>
- Narendrakumar, L., & Ray, A. (2022). Respiratory tract microbiome and pneumonia. In *Progress in Molecular Biology and Translational Science*, 192(1), 97–124.
- Proal, A. D., VanElzakker, M. B., Aleman, S., et al. (2023). SARS-CoV-2 Reservoir in Post-Acute Sequelae of COVID-19 (PASC). *Nature Immunology*, 24(10), 1616–1627.
- Ren, Z., Wang, H., Cui, G., et al. (2021). Alterations in the Human Oral and Gut Microbiomes and Lipidomics in COVID-19. *Gut*, 70(7), 1253–1265.
- Ridlon, J. M., & Gaskin, H. R. (2024). Another renaissance for bile acid gastrointestinal microbiology. *Nature Reviews Gastroenterology & Hepatology*, 21, 348–364.
- Seekatz, A. M., & Abt, M. C. (2025). Advances in Understanding the Pathogenesis of *Clostridioides difficile* Infection. *Infectious Disease Clinics of North America*, 39, 761–779.
- Vance, J., & Turner, N. A. (2025). Infection Prevention Approaches for *Clostridioides difficile*. *Infectious Disease Clinics of North America*, 39(4), 685–707.
- Van Seventer, J., & Hochberg, N. (2016). Principles of infectious diseases: transmission, diagnosis, prevention, and control. In *International Encyclopedia of Public Health* (Vol. 5, 2nd ed.), 22–39.
- Wilcox, M. H., Gerding, D. M., Poxton, I. R., et al. (2017). Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection. *New England Journal of Medicine*, 376(4), 305–317.
- Woo, S., Park, S. Y., Kim, Y., et al. (2020). The dynamics of respiratory microbiota during mechanical ventilation in patients with pneumonia. *Journal of Clinical Medicine*, 9(3), 638.
- Zakharkina, T., Martin-Loeches, I., Matamoros, S., et al. (2017). The dynamics of the pulmonary microbiome during mechanical ventilation in the intensive care unit and the association with occurrence of pneumonia. *Thorax*, 72(9), 803–810.
- Zollner, A., Meyer, M., Jukic, A., et al. (2024). The Intestine in Acute and Long COVID: Pathophysiological Insights and Key Lessons. *Yale Journal of Biology and Medicine*, 97(4), 447–462.
- Zuo, T., Zhang, F., Lui, G., et al. (2020). Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology*, 159(3), 944–955