International Journal of Zoology Studies
www.zoologyjournals.com
ISSN: 2455-7269
Received: 13-05-2025, Accepted: 12-06-2025, Published: 28-06-2025
Volume 10, Issue 2, 2025, Page No. 121-126

Host microbiome interaction in infectious disease progression

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Abstract
The human microbiota comprises many microorganisms that live in and on our bodies and are important for our health. When this community is disturbed, a condition known as dysbiosis, it has been linked to various diseases. Recent studies show that the microbiota can significantly influence the progression of infectious diseases. This review explores how the microbiota can both protect us from and contribute to infections, whether short-term or long-lasting, and the complications that can arise. We also discuss new research on how microbiota, hosts, and pathogens interact, and how environmental factors shape these relationships. By learning more about how the microbiota affects infectious diseases, we can find better ways to diagnose, prevent, and treat them.

Keywords: human microbiota, infectious diseases, co-morbidities, microbiota-host-pathogen interactions, environmental factors

Introduction

For a long time, research on infectious diseases focused on the germs that cause illness and the people who get sick. These findings helped scientists identify disease-causing agents and develop antibiotics, but overlooked the microbes that naturally live in our bodies. Now, we know that human and microbial cells are present in about equal numbers. This collection of microorganisms, including bacteria, fungi, viruses, and others, is called the microbiota [1]. These findings have changed our understanding of infectious disease research [2].

The human body functions like a complex ecosystem, with the gut one of the busiest habitats for microbes. The main bacteria in the gut are Firmicutes and Bacteroidetes, along with smaller groups such as Actinobacteria, Proteobacteria, and Verrucomicrobia [3]. These microbes help us digest food, produce vitamins, and support our immune system [4]. Factors such as how we were born, our diet, and early antibiotic use can influence which microbes live in our bodies [5].

A key role of the gut microbiota is to prevent harmful microbes from establishing a foothold, a process known as colonization resistance. The good bacteria in our gut take up space, leaving little room for outside pathogens. They also produce substances that kill or slow the growth of harmful bacteria [6] and help maintain a balanced immune system [7].

Gut microbes communicate with our body by releasing specific chemicals. For instance, when they break down dietary fibre, they create short-chain fatty acids (SCFAs) such as butyrate. These SCFAs provide energy to colon cells, help regulate inflammation, and influence how immune cells function [8].

When the gut microbiota is disturbed, a condition called dysbiosis can result from antibiotics, major dietary changes, or illness. Dysbiosis makes it harder for the gut to keep harmful microbes out, allowing pathogens such as *Clostridioides difficile* to grow and cause disease [9]. These harmful microbes can detect and exploit changes in the gut environment following disruption of the microbiota [10].

Some microbes that are usually harmless, called pathobionts, can become harmful if conditions change, such as when the immune system is weak or the gut barrier is damaged [11].

Gut microbes influence more than just our digestion. For example, the gut-lung axis is a two-way link in which gut microbes affect the immune system in the lungs, thereby altering our risk of respiratory infections like the flu and tuberculosis [13]. Gut microbes also signal the brain through the gut-brain axis.

Despite progress in this field, there is still much we do not understand. People's microbiomes can vary widely, making it difficult to define exactly what a "healthy" microbiome is. While we have identified links between some microbes and diseases, more research is needed to establish cause and effect. This review summarises what we know so far about how microbes influence infectious diseases, covering both their helpful and harmful roles.

The Protective Microbiota

A balanced microbiome plays an important role in defence against pathogens.

1. Fighting Invaders Directly

Our beneficial bacteria are not passive; they actively defend against pathogens. First, by occupying space along our gut lining, they leave little opportunity for harmful bacteria to adhere. Second, they produce specialised proteins called bacteriocins that target and kill related bacterial strains [6]. For instance, some bacteria produce a compound called thuricin CD, which specifically eliminates *C. difficile* while sparing other helpful bacteria [15]. This approach is more targeted than antibiotics, which can affect both harmful and beneficial bacteria.

2. Competing for Food

One of the simplest but most effective strategies is competition for nutrients. Our good bacteria are experts at eating whatever comes through our digestive system. When they have eaten everything, there is nothing left for invading pathogens to feed on.

Let us look at how this works with *C. difficile.* Our liver makes bile acids that help digest food. Some of these bile acids actually trigger *C. difficile* spores to awaken and begin

growing. Healthy gut bacteria convert these primary bile acids into secondary bile acids that actually stop *C. difficile* from growing [10,16]. Certain bacteria, such as *Clostridium scindens,* are particularly adept at this conversion [17]. When antibiotics kill these beneficial bacteria, the protective barrier breaks down, allowing *C. difficile* to thrive.

Table 1: How Gut Bacteria Use Food Competition to Stop Pathogens

Pathogen	What Helpful Bacteria Do	How It Stops the Pathogen	Reference
Clostridioides difficile	Change bile acids from germinating form to inhibiting form	Prevents spores from waking up; stops growth	[16]
Salmonella Typhimurium	Compete for iron using special molecules	Starves the pathogen of essential iron	[18]
E. coli O157:H7	Eat all available sugars	Leaves nothing for pathogen to eat	[19]
Citrobacter rodentium	Make SCFAs like butyrate	Strengthens gut barrier; directly inhibits pathogen	[20]

3. Training Our Immune System

Our gut microbes are like personal trainers for our immune system. They constantly provide low-level stimulation that keeps our immune cells ready but not overreacting [7]. The SCFAs they produce, especially butyrate, help generate regulatory T cells that prevent the immune system from attacking friendly bacteria [21].

Even more impressive, gut signals affect how many immune cells our bone marrow produces. Mice without gut microbes have fewer infection-fighting cells and are more vulnerable to Listeria infection [22]. The results show that our gut microbes influence the entire body's immune readiness, not just the gut.

The Dark Side

Remember how we said a healthy microbiome protects us? Well, when it has been disrupted, the opposite happens. The same community that protected us can now make us sick.

1. Antibiotics Create Opportunities

Antibiotics are the main cause of dysbiosis. They kill bad bacteria but also wipe out good ones. When the good bacteria die, nutrients that they normally consume become available. Pathogens such as *Salmonella* and *C. difficile* can acquire these nutrients and multiply rapidly [23]. Some pathogens even feed on byproducts produced by the few bacteria that survived antibiotic treatment [24]. Antibiotics can end up helping the germs they're supposed to eliminate.

2. Inflammation Helps Pathogens

When we get an infection, our body causes inflammation to fight it. However, inflammation changes the gut environment in ways that help certain pathogens. During inflammation, immune cells release chemicals that create oxygen in the normally oxygen-free gut [25]. It kills many beneficial bacteria that do not require oxygen. However, pathogens such as *Salmonella* and some *E. coli* can use the oxygen and other chemicals produced during inflammation to grow better [26]. The body's defence mechanism accidentally creates perfect conditions for the enemy.

3. Friendly Bacteria That Turn Nasty

Some bacteria that normally live peacefully in us can cause disease under certain conditions. These are called pathobionts. For example, *Fusobacterium nucleatum* normally lives in our mouth without problems. However, if it gets into our gut and conditions are right, maybe because of inflammation or a weakened gut barrier, it can promote colon cancer by attaching to gut cells and turning on cancer-causing signals [27]. Similarly, some E. coli strains that are usually harmless can cause problems in people with Crohn's disease [30].

Table 2: Friendly Bacteria That Can Turn Nasty

Bacteria	Diseases It Can Cause	How It Causes Trouble	When It Turns Bad	Reference
Fusobacterium nucleatum	Colon cancer	Attaches to cells; turns on cancer signals; hides from the immune system	Damaged gut lining; tumour environment	[27]
Bacteroides fragilis (certain types)	Inflammatory bowel disease; colon cancer	Makes a toxin that damages the gut lining and causes inflammation	Genetic susceptibility; disrupted gut community	[29]
E. coli (AIEC type)	Crohn's disease	Sticks to gut cells; survives inside immune cells	Genetic mutations (like NOD2); damaged barrier	[30]
Enterococcus faecalis	Surgical site infections; heart infections	Makes harmful oxygen molecules; sticks to surfaces	Weak immune system; medical implants	[31]

The Gut-Lung Connection: How Gut Bugs Affect Breathing

One of the most fascinating discoveries is that our gut microbes affect how well our lungs fight infection. It is called the gut-lung axis [13].

When antibiotics or a poor diet disrupts our gut microbes, our lungs become more vulnerable to infections such as the flu, pneumonia, and tuberculosis. How does this work? The SCFAs made by gut bacteria travel through our bloodstream to our bone marrow, where they influence the development of immune cells that later travel to our lungs [32]. These cells are then ready to fight respiratory infections.

For example, a substance called desaminotyrosine (DAT), produced by gut bacteria, helps protect against the flu by priming lung immune cells to respond more effectively [33]. In tuberculosis, people with lower levels of *Lactobacillus* and *Bifidobacterium* in their gut have weaker immune responses and are more susceptible [35]. Even non-tuberculous mycobacterial lung disease is linked to gut bacterial imbalances [14].

Table 3: How Gut Bacteria Affect Lung Infections

Lung Infection	Gut Bacteria Changes Linked to More Disease	How It Might Work	Reference
Influenza	Loss of certain *Clostridia* bacteria	Less desaminotyrosine; weaker interferon responses	[33]
Pneumonia (Streptococcus)	Antibiotic-caused disruption	Weakened lung immune cells	[34]
Tuberculosis	Low *Lactobacillus* and *Bifidobacterium*	Disrupted T-cell balance; poorer granuloma formation	[35]
NTM lung disease	Low *Prevotella* and *Bifidobacterium*	Weakened interferon responses; SCFA deficiency	[14]
RSV in infants	Low *Bifidobacterium* and *Lactobacillus*	Skewed immune responses	[36]

New Treatments: Fixing the Microbiome

Understanding that gut microbes affect infections has led to new treatment ideas. Instead of just killing pathogens, we can try to restore healthy microbial communities.

1. Faecal Microbiota Transplantation

The most successful microbiome treatment to date is faecal microbiota transplantation (FMT) for recurrent *C. difficile* infection. It involves transplanting stool from a healthy donor into a patient with recurrent *C. difficile* infection. It works amazingly well, curing over 90% of cases [39]. FMT restores the diverse gut community, bringing back bacteria that convert bile acids, compete for nutrients, and produce protective substances [40]. It proves that restoring a healthy microbiome can treat infection.

2. Probiotics, Prebiotics, and Designer Consortia

Simple probiotics (taking one or a few bacterial strains) have shown mixed results. However, researchers are now developing more sophisticated approaches. Defined bacterial consortia are mixtures of specific bacteria selected to restore particular functions, such as bile acid metabolism [17]. Prebiotics are food ingredients that feed good bacteria. By increasing our fibre intake, we can boost SCFA production and strengthen our defences [8].

3. Targeting Pathogen Weaknesses

Understanding how pathogens exploit dysbiosis has revealed new treatment targets. Instead of broad-spectrum antibiotics, we could develop drugs that specifically block pathogen germination or nutrient uptake. For *C. difficile*, compounds that block spore germination could prevent infection without harming other bacteria [41]. Bacteriophages, viruses that specifically kill bacteria, offer another precision approach**.**

Table 4: New Microbiome-Based Treatments

Treatment	How It Works	What It Treats	Development Stage	References
Fecal transplant	Restores the whole gut community	Recurrent *C. difficile*	Approved and used clinically	[39]
Bacterial consortia	Restores specific key functions	*C. difficile*; drug-resistant bacteria	Advanced trials	[17]
Phage therapy	Specifically kills target bacteria	Device infections: *C. difficile*	Early trials; compassionate use	[42]
Prebiotic fiber	Boosts SCFA production	Gut and lung infections	Preclinical and early clinical	[8]
Bile acid blockers	Prevents *C. difficile* spore germination	*C. difficile*	Preclinical	[41]
Iron competition	Starves pathogens of iron	*Salmonella* and others	Preclinical	[18]

Polymicrobial Infections: When Communities Cause Disease

Traditional thinking focused on a single germ causing a single disease. However, many chronic infections involve entire communities of microbes working together in biofilms—slimy communities attached to surfaces [43].

1. Biofilms and Teamwork

In conditions like cystic fibrosis, chronic wounds, and on medical devices, multiple species live together in biofilms. They cooperate, sharing nutrients and protecting each other from antibiotics [44]. They communicate through quorum sensing, a chemical signalling system that enables them to coordinate their behaviour, much like a swarm of bees [45]. Within biofilms, bacteria can also swap genes, spreading antibiotic resistance [46].

2. New Ways of Thinking

This polymicrobial view requires new diagnostic approaches. Instead of culturing one bacterium, we need methods that capture entire communities [47]. Treatment should target the community, not just individual members. Biofilm-disrupting enzymes, quorum-sensing blockers, and phages that penetrate biofilms offer new possibilities [12].

Table 5: Examples of Polymicrobial Infections

Infection	Common Microbes Involved	How They Work Together	Result	References
Cystic fibrosis lung	*Pseudomonas*, *Staphylococcus*, others	Share food; change antibiotic sensitivity; stronger biofilms	Progressive lung damage; treatment failure	[44]
Chronic wounds	*Staphylococcus*, *Pseudomonas*, anaerobes	Boost each other's harmful effects; delay healing	Non-healing wounds; spread of infection	[49]
Periodontitis	"Red complex" bacteria	Stick together; cooperate metabolically; evade immunity	Tooth and bone destruction	[50]
Medical device infections	Staphylococci, *Candida*, others	Form biofilms on devices; resist antibiotics	Persistent infection; device removal needed	[43]
Bacterial vaginosis	*Gardnerella*, *Atopobium*, others	Form biofilms; produce amines together	Pregnancy complications; recurrence	[51]

What Shapes Our Microbiome?

1. Antibiotics

Antibiotics save lives but can harm microbiomes. Even a single course can decrease diversity for months [23]. Use of antibiotics early in life is especially concerning, as it is associated with increased risks of inflammatory bowel disease, asthma, and obesity later [52]. This has led to efforts to develop more targeted antibiotics and better diagnostic tests, ensuring antibiotics are used only when truly necessary.

2. Diet

Diet powerfully shapes your microbiome. High-fibre diets feed SCFA-producing bacteria like *Faecalibacterium* and *Bifidobacterium*, promoting anti-inflammatory effects and stronger gut barriers [8]. Western diets high in fat and sugar but low in fibre promote dysbiosis, reducing diversity and increasing harmful Proteobacteria [53]. A high-fibre diet protects against certain gut infections in mice, while high-sugar diets increase susceptibility [20]. Dietary changes could be a simple, accessible way to boost resistance to infection.

3. Our Genes Matter Too

Your genetic makeup also influences your microbiome. People with certain immune gene variations (such as NOD2 mutations) have distinct microbiomes and a higher risk of Crohn's disease [30]. These genes normally help control bacterial overgrowth. Understanding how host genetics affects microbiome composition and infection risk could enable personalised prevention strategies [54].

Conclusion

Our understanding of infectious diseases has grown tremendously. We've moved from a simple "germ causes disease" model to a much richer understanding that includes the trillions of microbes living on and in us. These microbes aren't passive passengers; they're active partners that profoundly influence whether we get sick, how sick we get, and how well we respond to treatment.

A healthy microbiome protects us through multiple strategies. Good bacteria physically occupy space, compete for food, produce antimicrobial compounds, and constantly train our immune systems. They convert bile acids to forms that inhibit pathogens, produce SCFAs that strengthen our gut barrier and guide immune responses, and maintain a state of readiness throughout our body. This protective role makes the microbiome an essential part of our defence system, not just a collection of bystanders.

But this protection depends on balance. When disrupted by antibiotics, poor diet, or illness, the same community that protected us can become a source of vulnerability. Dysbiosis creates opportunities for pathogens to flourish. The inflammation our body generates to fight infection can accidentally fuel certain pathogens. And under permissive conditions, normally benign bacteria can become pathobionts that actively contribute to disease. This dual nature, protective in health, permissive in dysbiosis, reveals the delicate balance we must maintain.

The microbiome's influence extends far beyond the gut. Through axes like the gut-lung connection, signals from gut bacteria shape immune responses throughout the body, affecting our susceptibility to respiratory infections, systemic diseases, and possibly even vaccine responses. This systemic reach means that maintaining a healthy gut microbiome supports whole-body health.

This new understanding has already produced one spectacular therapeutic success: faecal microbiota transplantation for recurrent *C. difficile* infection. This proof that restoring a healthy microbiome can cure disease has energized efforts to develop more refined approaches—defined bacterial consortia, prebiotics, phage therapy, and pathogen-specific interventions that exploit our growing knowledge of microbial metabolism and ecology.

Looking ahead, we must embrace the complexity of polymicrobial communities and their biofilm lifestyles. This demands new diagnostic tools capable of capturing community dynamics and new treatments targeting community properties rather than individual species. The infectome framework challenges us to think ecologically about chronic infections.

Despite remarkable progress, substantial challenges remain. The enormous variability between individuals complicates efforts to define universal therapeutic targets. Proving causality for specific microbial functions in human disease requires continued rigorous research. The interplay between host genetics, diet, environment, and microbiome demands integrated approaches and long-term studies.

As we continue unravelling how the microbiome shapes infectious disease, the ultimate goal remains clear: translate this knowledge into practical approaches that prevent infection, improve treatment outcomes, and ultimately help people live healthier lives. The microbiome is no longer a forgotten organ but a central player in infection, offering both challenges to our traditional views and unprecedented opportunities for therapeutic innovation.

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