

# Fundamental Factors Affecting the Development and Function of the Pediatric Microbiome

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## Abstract

Recent technological advances have spawned a better understanding of the human microbiome. This review will highlight certain current and significant findings regarding the development and function of the human microbiome in the pediatric population. Research had been conducted on the structural and functional capacity of the microbiome in the healthy state as well as disease states. Emerging technologies, developed mainly from the Human Genome Project and the NIH-funded Human Microbiome Project (HMP), have been applied to evaluate the pediatric microbiota. As the functional interactions between the host and its microbiome are analyzed in more detail, science is beginning to understand better these interactions and how they impact overall health. A more sophisticated understanding of the role of the microbiome in health and disease can be achieved with studies that further characterize the functions of the microbiome and the host-microbe mechanistic interactions [1].

**Keywords:** Archaea; Commensal; Dysbiosis; Firmicutes; Inflammation; Microbiome; Microbiota; Oligosaccharides; Pediatric; Probiotic; Proteobacteria

## Abbreviations

AMR	:	Antimicrobial Resistance
CD	:	Crohn's Disease
FDA	:	Food and Drug Administration
GALT	:	Gut-Associated Lymphoid Tissue
GI	:	Gastrointestinal
HMO	:	Human Milk Oligosaccharides
HMP	:	Human Microbiome Project
IBD	:	Inflammatory Bowel Disease
IgA	:	Immunoglobulin A
NEC	:	Necrotizing Enterocolitis
PRR	:	Pattern Recognition Receptors
TLR	:	Toll-Like Receptor
UC	:	Ulcerative Colitis
WHO	:	World Health Organization

## Introduction

The host-intestinal microbiota relationship is generally symbiotic. Torrazza & Neu (2011) established the relationship to involve an intricate system promoting health and modulating the immune response. The human microbiome is composed of bacteria, viruses, archaea, and eukaryotic microbes which contribute to metabolic functions, protect against pathogens, and modulate the immune system. Shreiner, Kao & Young (2015) found it to play a significant role in the physiology of health and pathophysiology of disease.

## Discussion

### Functions of the Intestinal Microbiota

The essential roles of the intestinal microbiota include metabolism, nutrition, immunological functions, and defense against pathogens. Thus, any alterations of the microbiota may lead to dysbiosis and disease in infancy as well as late into childhood as depicted in Table 1 below [2]. Intestinal bacteria play a vital role in early development of the gut's mucosal immune system regarding its physical components and functions; and continue to do so throughout and into later life. Gut-associated lymphoid tissue (GALT) is stimulated by bacteria to produce antibodies in response to pathogens. These antibodies allow the immune system to recognize and fight the harmful bacteria without compromising

the beneficial bacteria.

Recently, Toll-like receptors (TLRs) have been found to be expressed by gut bacteria via various intestinal cell types including the gut epithelium [2]. TLRs are pattern recognition receptors (PRRs) that provide the intestine with the ability to discriminate between pathogenic and beneficial bacteria. Once these TLRs identify the pathogen that has crossed a mucosal barrier, they trigger a set of responses that act against the pathogen. Research continues to better understand the effects of the intestinal microbiota specific to secretory IgA, TLRs, and other PRRs. The study of the presence and activation of the human microbiota will contribute to a better understanding of the inflammatory cascade that leads to certain diseases, such as necrotizing enterocolitis (NEC) or systemic inflammation associated with multiple organ dysfunction [2].

### The Significance of Early Microbiome Development

The development of the gut microbiome is vital to the maturation of the intestinal immune system. One of the functions of the immune system is to maintain an anti-inflammatory state in the gut especially during exposure to innocuous antigens from commensals, hormones, and food. For the immune system to effectively carry out its complex function, the diverse cell types must interact.

The pattern recognition of normal, developed intestinal flora delimits the intrinsic bacteria from activating the immunological response. Oral tolerance is a process in which bacteria can influence the immune system to be less sensitive to an antigen once it has been ingested. This oral tolerance is mediated by the gastrointestinal immune system and the liver. Oral tolerance can inhibit overreacting of the immune response, such as those reactions observed in allergies and autoimmune disease [2].

Healthy microbiota	Alterations of microbiota or dysbiosis	
	Early in the neonate	Later in childhood
<b>Stimulates the GALT and antibody production</b>		
Metabolize nutrients	NEC (Necrotizing Enterocolitis)	Obesity
Defense and barrier against pathogens	Sepsis	Diabetes
Modulation of inflammatory response and intestinal permeability	Diarrhea/ Malnutrition	Allergies, asthma, Metabolic syndrome

**Table 1:** Intestinal microbiota in the neonate [2].

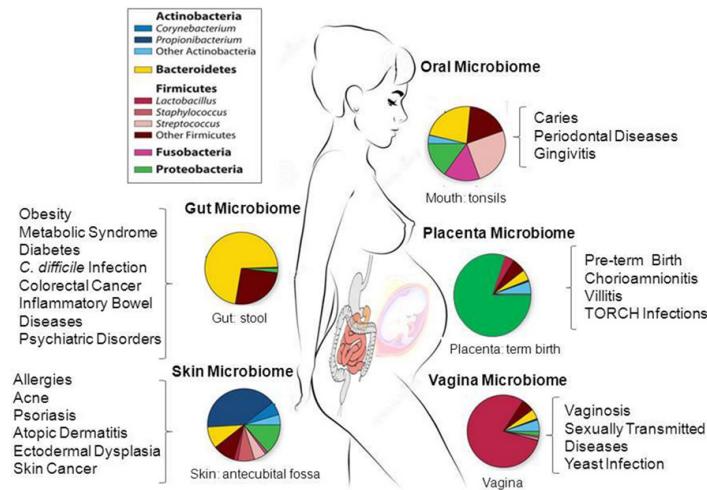
### The Microbiota of the Fetus and Newborn

An individual's microbiome has been shown to be somewhat stable over time; however, there is some variability in the extremes

of age and among individuals. Also, various factors could affect the composition of the microbiome, e.g., diet and environment [1]. Growing evidence indicates that the intestinal microbiota play a fundamental and essential role in postnatal immune system development.

Epidemiological data suggest that certain diseases (such as atopic dermatitis, asthma, type 1 diabetes, and food allergies) appear more often in infants born via cesarean delivery rather than via vaginal delivery. Therefore, it stands to reason that if the intestinal flora develop differently depending on the mode of delivery, the postnatal development of the immune system may also be different [2].

Another importunate consideration is most mothers undergoing cesarean deliveries are also treated with antibiotics; studies in adults have suggested that treatment with antibiotics may affect the gastrointestinal tract for years [3]. The enteric microbiota composition in the early days of life, therefore, seems to contribute significantly to achieving and maintaining good health in the years to come. Thus, it is central to identify the intestinal ecosystem during the early developmental stages [2].



**Figure 1:** The taxonomic distribution, prevalence, and abundance of microbial taxa that inhabit healthy human body sites as defined in the Human Microbiome Project [4].

### Probiotics and the Pediatric Microbiome

According to the World Health Organization (WHO), the probiotic is defined as "a live microorganism, which when administered in adequate amounts, confers a health benefit on the host". Studies have shown that microbial components of certain foods may, in fact, promote health. Specifically, probiotics are thought to modulate intestinal microflora, reduce intestinal permeability, and decrease proinflammatory cytokines while increasing anti-inflammatory cytokines [2]. For these reasons, in the past two decades, there has been growing interest in the

potential benefits of certain types of probiotics. Currently, the Food and Drug Administration (FDA) in the United States does not have a system for the monitoring of probiotics do not need FDA approval. Previous studies had shown that some probiotics are more beneficial than others [5].

### **Antibiotics and the Pediatric Microbiome**

The gut microbiome is in constant flux; the community composition continuously adapts to environmental exposures and host developmental changes. This adaptation is essential for maintaining gut homeostasis; however, drastic changes (such as those induced by antibiotics) can potentially lead to adverse health consequences. This is of concern since antibiotics are by far the most common prescription drug given to children.

The emergence of antimicrobial resistance (AMR) has been associated with antibiotic use. The WHO has identified AMR as “one of the three greatest threats to human health” [6]. Broad-spectrum antibiotics are designed to eradicate multiple bacterial taxa. Subsequently, the microbiome may be impacted by a loss of vital taxa. This loss is detrimental to homeostasis and the development of the immune system; a loss of biodiversity can result in adverse health risks, such as dysbiosis. Pediatric dysbiosis is characterized by such drastic changes in the microbial community and has been implicated in microbiome imbalance (dysbiosis) in numerous diseases [4].

Epidemiological studies have identified associations between antibiotic use in early infancy and development of various diseases later in life, e.g., obesity, diabetes, and asthma. Longitudinal studies of antibiotic usage have demonstrated profound short-term and long-term effects of antibiotics on the diversity and composition of the gut microbiota [6].

### **Major Influences on Microbiome Development**

Diet plays a significant role in the colonization of the modern infant gastrointestinal (GI) tract. Vast compositional differences have been noted between the intake of human milk and infant formulas. Of note, beneficial *Lactobacillus* and *Bifidobacterium* species were commonly found in a higher proportion in the intestinal microbiota of breast-fed infants compared to formula-fed infants [2]. Potentially harmful *Enterococci* and *Enterobacteria* are the predominant bacteria found in the gut of the formula-fed infant.

The human milk microbiome does change over time and has also been found to depend on the mother’s weight. Breast milk from obese mothers is less diverse than breast milk from non-obese mothers. Human milk oligosaccharides (HMOs) are milk-borne prebiotics that modulate bacteria in the GI tract. HMOs are sugars produced solely for consumption by microbes.

Another antimicrobial in human milk that influences microbes within the GI tract is secretory immunoglobulin A (IgA). In a study by Vangay et al. (2015), IgA was found to provide antigen-specific protection against microbes that the mother has already encountered as well as innate immune proteins that harbor bactericidal properties [6].

As previously mentioned, the mode of delivery (birth) had an impact on the microbiome of infants. The microbiomes of vaginally delivered infants consist mostly of *Lactobacillus*, *Prevotella*, *Atopobium* or *Sneathia*; whereas, the microbiomes of cesarean section delivered infants contain *Staphylococcus* and, to a lesser degree, *Bifidobacterium* [6].

### **Inflammation Modulated by Microbial Components**

Studies were conducted on epithelial cells in infant formula-fed rodent models. Results suggested that dead microbes might be as active as live microbes in modulating excessive inflammatory stimuli [2]. Determining whether low-grade stimulation of these receptors or signaling pathways induces tolerance or a protective effect requires further study. Additional investigation is needed to identify the therapeutic potential of pharmaceutical or dietary interventions necessary to alter the accessibility of colonizing bacteria to receptors.

### **The Role of the Microbiome in Pediatric GI Disorders**

The diversity of the oral microbiome in pediatric inflammatory bowel disease (IBD) results in a marked decrease in both overall microbial diversity as well as specific phylum levels in patients with Crohn’s Disease (CD). Alterations in the oral microbiome in both local and systemic disease were identified indicating oral microbial biomarkers may be present in certain disease conditions. Experimental models of germ-free mice suggest the host-microbe interaction is a significant factor in the development of IBD.

The oral mucosa (an immunologically active surface) has been noted to support increased cytokine production in children with CD compared to healthy control patients. Since the oral cavity serves as a “window” into the intestinal tract, the oral cavity provided an excellent opportunity to study the complex interaction of the host immune system and microbiome at the epithelial interface [7]. Distinct shifts in the enteric microbiota, as seen in dysbiosis, has been observed in patients with CD and ulcerative colitis (UC). The intestinal microbiome in diseased states appeared to lose commensal organisms that typically characterize health. This lack of diversity is a common finding in IBD microbial studies.

In a study by Lewis et al. (2015) [8], the environmental stresses experienced by CD patients were associated with changes in microbial taxonomy. It was shown that dysbiosis involved differences in microbial gene representation, increases in fungal

representation, and higher levels of human DNA in the stool. Antibiotic exposure was identified as a risk factor for new-onset CD and was strongly associated with dysbiosis. It was found that dysbiosis in CD extended beyond bacteria to include fungi; the dysbiosis resulted from a combination of inflammation, antibiotic exposure, and dietary changes. The characteristics of dysbiosis include an expansion of Proteobacteria with a decrease in Firmicutes; also, a decrease in community richness of the microbiota. It is not yet known whether dysbiosis secondary to inflammation is quickly reversible.

## Conclusion

Medical research has just begun to establish a core of microbiota that is helpful in defining a state of health in complex environments like the pediatric GI tract and oral microbiome. It is an exciting and dynamic period in the study of the microbiome due to recent technological advancements and rapidly expanding knowledge [1]. It seems likely that the organisms that define a healthy microbiome confer protective mechanisms to the host. It can also be posited that, in the absence of this diversity of organisms, pathogens can arise and flourish [7]. A crucial consequent step is to investigate the various functions of the pediatric microbiome; in particular, how these functions pertain to health and disease. Such studies will provide additional insights into host-microbiome interactions allowing for the development of therapies that will target the microbiome to maintain health and to treat a variety of diseases [1].

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## Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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