

# Let Them Eat Dirt: Raising Children with Their Microbes

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Ever since Robert Koch and Louis Pasteur showed that germs cause infectious diseases 125 years ago, society has been at war with microbes. Sewer and sanitation systems were developed and garbage collection established. Life-saving antibiotics became available near the end of the Second World War. Vaccines were developed to prevent many common childhood diseases. Society went on a campaign against microbes using sanitation and other hygienic methods. Collectively, this major hygiene campaign did a wonderful job of ridding the developed world of disease-carrying germs: “Cleanliness is next to Godliness.” “The only good microbe is a dead one.” “Cover your mouth when you cough.” This remarkable hygiene battle resulted in spectacular increases in life expectancy, and infant mortality plummeted over the past century, dropping from about 1 in 10 to 1 in 200.

However, we now realize that this eradication of microbes has unexpected consequences. Asthma rates have gone from about 1% to over 10% of all children.<sup>1</sup> In the past five years, we have witnessed unprecedented growth in childhood obesity, in addition to the continuing adult obesity epidemic. The rates of inflammatory bowel diseases, mental health disorders such as depression, anxiety, and even autism continue to increase rapidly. While the rates of nearly all infectious diseases continue to decline, the opposite is occurring in the non-infectious diseases. We haven’t changed genetically in 50 years. It turns out that our war on microbes is having unforeseen consequences as collateral damage.

There are at least as many microbes in and on you as human cells, and they encode greater than 93% of the DNA in and on us.<sup>2</sup> We are more microbe than human: *H. sapiens* DNA comprises less than 7% of the total genes in a human being! Even precision medicine is in trouble; humans are more than 99.9% identical genetically, yet we each have a unique set of microbes, sharing less than half with any other person.<sup>2</sup> We are colonized at birth, and even that first birthday present—fecal and vaginal microbes from Mom—is critical for setting us up for life (Fig 1).<sup>3</sup> If you are born by Cesarean section (C-section), as over one quarter of Canadian and American children now are, you will miss out on these important microbes and this increases one’s chances for allergies and asthma by 20% later in life.<sup>4</sup> This 20% difference in allergy and asthma risk is also observed in those who were breastfed versus bottle-fed, and those who live on a farm versus in a city.<sup>4</sup> These factors result in exposure to

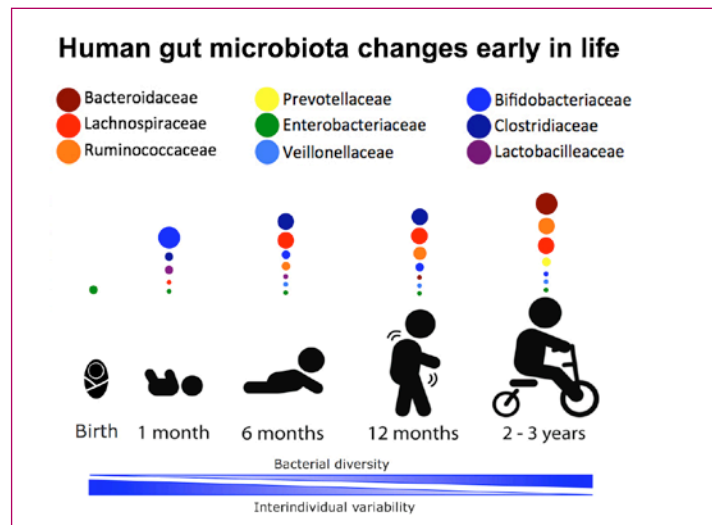


Fig 1. Stages of microbial colonization of the infant and child intestine.<sup>3</sup>

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different microbes. Even owning a dog drops the chance of getting asthma by 20% (cats have no effect).<sup>4</sup> With all this fascinating epidemiology comes the need to do more science.

Using a murine asthma model we were able to show that the gut microbiota has a profound influence on asthma.<sup>5</sup> Further studies showed that there was an early life period which was critical for later asthma susceptibility.<sup>6</sup> This effect seemed to be mediated by affecting how the immune system developed, including affecting regulatory T cells. This work identified a ‘critical window’ early in life where gut microbial changes (dysbiosis) are most influential in experimental asthma.

In a more recent study, we compared the gut microbiota of 319 subjects enrolled in the **C**anadian **H**ealthy **I**nfant **L**ongitudinal **D**evelopment (CHILD) Study, and showed that infants at risk of asthma exhibited transient gut microbial dysbiosis during the first 100 days of life.<sup>7</sup> The relative abundances of the bacterial genera *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia* were significantly decreased in children at risk of asthma. This reduction in bacterial taxa was accompanied by a reduced fecal production of acetate (a short-chain fatty acid [SCFA]) and dysregulation of enterohepatic metabolites. Inoculation of germ-free mice with these four bacterial taxa ameliorated airway inflammation in their adult progeny, demonstrating a causal role of these bacterial taxa in averting asthma development.<sup>7</sup>

Most recently, we compared the bacterial and eukaryotic gut microbiota of 97 infants from the coastal community Las Esmeraldas, Ecuador at 3 months of age by 16S and 18S sequencing (manuscript submitted). Bacterial metagenomes were predicted from 16S rRNA data using PICRUSt (**P**hylogenetic **I**nvigation of **C**ommunities by **R**econstruction of **U**nobserved **S**tates), and categorized by function using KEGG Orthology (**K**yoto **E**ncyclopedia of **G**enes and **G**enomes). The concentration of fecal SCFAs was determined by gas chromatography. This study found marked bacterial and fungal dysbiosis of the gut of 3-month-old babies at a high risk of asthma in a coastal Ecuadorian population. The alterations were taxonomically different yet functionally similar to the dysbiosis previously found in Canadian babies. This study again strongly supports the importance of an early critical window of microbial dysbiosis in the context of allergy and asthma.

Environmental enteropathy (EE) is a subclinical chronic inflammatory disease of the small intestine, and has a profound impact on the persistence of childhood malnutrition worldwide. However, the etiology of the disease remains unknown but animal models were lacking, hindering mechanistic studies. We recently showed that early-life consumption of a moderately malnourished diet low in protein and fat, in combination with oral exposure to commensal *Bacteroidales* species and *Escherichia coli*, remodels the murine small intestine to resemble features of EE observed in humans.<sup>8</sup> We also found profound changes on the small intestinal microbiota, metabolite and intraepithelial lymphocyte composition, along with the susceptibility to enteric infection. These findings provide evidence indicating that both diet and microbes combine to contribute to the etiology of EE, and that this novel murine model can be used to elucidate the mechanisms behind this understudied disease.

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Collectively, we must rethink our relationship with our microbes and establish a balance between hygiene and exposure to beneficial microbes. Each generation gets cleaner, but the diversity and kinds of microbes in and on our bodies are decreasing rapidly. We are depriving the body of a critical part of its normal function, and the results are reflected in both health and disease. Ironically, because of our assault on microbes, some microbes could become endangered species, yet they have been an essential part of our evolution for millennia. We can't return to the wider range of microbes (and infectious diseases) of our great grandparents. We can, however, embrace microbes for our own good, as we rebalance hygiene with healthy microbes.

What can we do about this? We should think about how our communities, playgrounds, and time at school are designed to allow children access to ground-level play and outdoor learning. Antibiotics should be reserved for infectious diseases that clearly require treatment, and not squandered on colds, flus, and other conditions for which they are of no benefit. Attention to this is required ecosystem-wide: in medical care, dentistry, veterinary medicine, and agriculture. Finally, serious research is required to get us past our current superficial approach to probiotics. We need to understand which microbes are of health benefit, and how and when they can be successfully introduced to best benefit health. The future of health, wellness, and medical care will include our microbes, providing new tools to hopefully increase our health and longevity, long after major threats from germs have been mostly banished.

### References

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