Review

Biology

The Role of Gut Virome in the Overall Population Health

Walla Vincent*
University of Florida, 300 SW 13th Street, P.O. Box 113150, Gainesville, FL 32601, USA
*: All correspondence should be sent to: Dr. Walla Vincent
Author's Contact: Dr. Walla Vincent, Ph.D., E-mail: walla.vincent@aol.com
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The gut virome, comprising viruses that inhabit the human gastrointestinal tract, has emerged as a crucial but often overlooked component of the microbiome. While bacteria have historically received the most attention in health research, viruses—particularly bacteriophages—play fundamental roles in shaping microbial ecosystems, modulating immunity, and influencing host physiology. The gut virome interacts with bacterial populations by regulating their abundance and diversity, thereby affecting metabolic pathways and gut homeostasis. Evidence also suggests that viral communities influence susceptibility to chronic diseases, including inflammatory bowel disease, obesity, diabetes, and even neurological disorders. Beyond individual health, the virome contributes to population-level resilience against pathogens by maintaining microbial balance and supporting immune adaptation. However, much of the gut virome remains uncharacterized due to technological challenges in sequencing and interpretation. Understanding its role in overall population health could open new avenues for diagnostics, preventive medicine, and therapeutic strategies aimed at promoting sustainable well-being.

Keywords: Gut Virome; Population; Immunity; Composition; Overall Health

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Introduction

The human gut is home to an extraordinary and diverse community of microorganisms that together shape health and disease. While bacteria have traditionally occupied center stage in microbiome research, growing attention is now being directed toward the gut virome, the vast collection of viruses—primarily bacteriophages—that coexist within the gastrointestinal tract (Focà et al., 2015). Far from being passive passengers, these viruses actively participate in maintaining microbial equilibrium, influencing host immunity, and shaping physiological processes that extend far beyond the gut itself (Scarpellini et al., 2015).

The gut virome is dynamic, adapting across the lifespan in response to diet, environment, geography, antibiotics, and infec-

tion. Bacteriophages, which infect and regulate bacteria, serve as powerful modulators of microbial communities by controlling bacterial population dynamics and facilitating horizontal gene transfer (Boling et al., 2020). In this way, they indirectly affect digestion, nutrient absorption, and the production of metabolites essential for human health. Eukaryotic viruses, although less abundant, also influence gut physiology, sometimes through pathogenic mechanisms but often through more subtle interactions with the immune system (Gao et al., 2022).

At the population level, the gut virome may hold profound implications for global health. Variations in viral communities have been associated with disorders such as inflammatory bowel disease, obesity, diabetes, and even neurological and psychiatric conditions (Desselberger, 2021). Moreover, disruptions of the virome can weaken microbial resilience, leaving populations more vulnerable to infections and chronic illnesses (Khalil et al., 2024). Despite these insights, much of the virome remains poorly characterized due to the complexity of viral genomes and limitations in sequencing technology.

As research advances, the gut virome is emerging not as a marginal element but as a central determinant of health. Investigating its role in maintaining microbial balance, modulating immunity, and influencing disease susceptibility could transform strategies in public health, preventive care, and personalized medicine.

Composition and Diversity of the Gut Virome

The human gut is a vast and complex ecosystem where trillions of microorganisms coexist in a finely balanced symbiosis that profoundly influences human health. Within this intricate microbial landscape, bacteria have historically been the primary focus of research, but an equally important and often overlooked component is the gut virome (Nabi‐Afjadi et al., 2023). The virome encompasses the entire collection of viruses inhabiting the gastrointestinal tract, including bacteriophages that infect bacteria, eukaryotic viruses that interact directly with host cells, and other viral elements such as endogenous retroviruses embedded within the human genome. The composition and diversity of this virome are extraordinarily dynamic, reflecting the interplay of microbial ecology, host physiology, diet, environment, and immune function (Clemente et al., 2012). Understanding the makeup of the gut virome is essential not only for illuminating its contribution to individual health but also for appreciating its broader role in population health and disease susceptibility.

The most abundant and well-characterized members of the gut virome are bacteriophages, viruses that specifically infect bacteria. These phages exert profound influence on the gut microbiome by regulating bacterial abundance, shaping community composition, and facilitating horizontal gene transfer (Ogilvie & Jones, 2015). Unlike lytic phages, which destroy their bacterial hosts during replication, temperate phages can integrate into bacterial genomes as prophages, thereby modifying host metabolism and conferring new traits (Elois et al., 2023). Such interactions introduce layers of complexity into the gut ecosystem, as phages act as regulators of bacterial populations while simultaneously serving as reservoirs of genetic diversity (Boling et al., 2020). In fact, bacteriophages are estimated to outnumber bacteria in the gut by at least an order of magnitude, suggesting that they form a dominant but hidden axis of microbial ecology.

Eukaryotic viruses, though less abundant, contribute another dimension to the virome's composition. These include both pathogenic viruses such as rotavirus, norovirus, and adenovirus, as well as viruses that establish asymptomatic or persistent infections (Foc à et al., 2015). Some eukaryotic viruses interact directly with gut epithelial cells or immune cells, influencing immune responses in ways that extend beyond the intestine. For example, certain enteric viruses can modulate the development of innate and adaptive immunity, potentially compensating for the absence of commensal bacteria in germ-free organisms (Arrieta & Finlay, 2012). This highlights the virome's capacity not only to shape microbial communities but also to interact with the host at fundamental immunological levels.

In addition to bacteriophages and eukaryotic viruses, the gut virome also includes endogenous retroviral elements, remnants of ancient viral infections that have become permanently integrated into the human genome (Cadwell, 2014). Although many of these elements are inactive, some can influence gene expression and immune regulation, adding yet another layer of viral influence to host biology. These endogenous sequences blur the line between virome and genome, reflecting a deep co-evolutionary history in which viruses have left lasting imprints on human physiology (Desfarges & Ciuffi, 2012).

The diversity of the gut virome is immense, and much of it remains uncharacterized. High-throughput sequencing and metagenomics have revealed that the majority of viral sequences recovered from gut samples do not match any known reference genomes, forming what researchers call the "viral dark matter" (Fitzgerald et al., 2021). This vast reservoir of unknown sequences suggests that the true diversity of the gut virome far exceeds current knowledge. The challenge arises from the fact that viruses lack universally conserved genetic markers, such as the 16S ribosomal RNA gene used for bacteria, making viral classification and identification far more complex. As a result, the landscape of the gut virome is still being mapped, with new viral families and lineages continuing to be discovered.

The composition of the gut virome is not static but changes dynamically across the human lifespan. In infants, the virome is relatively simple but rapidly diversifies as the microbiome matures (Beller & Matthijnssens, 2019). Early life exposures, including delivery mode, breastfeeding, antibiotic use, and environmental contact, strongly shape the developing virome (Pargin et al., 2023). Interestingly, bacteriophages are often among the earliest colonizers, arriving even before many bacterial populations are fully established. During childhood and adolescence, the virome expands in complexity, paralleling the diversification of bacterial communities (Beller et al., 2022). In adulthood, the virome stabilizes but continues to adapt to dietary patterns, lifestyle factors, and environmental exposures (Xiao et al., 2021). In elderly populations, the virome often shifts again, reflecting changes in immune competence, comorbidities, and microbial community structure (Ogilvie & Jones, 2015). These age-related dynamics underscore the virome's responsiveness to both intrinsic and extrinsic influences.

Diet represents one of the most powerful modulators of

gut virome composition. Dietary changes alter bacterial populations, which in turn affect the phages that depend on them for replication. High-fat or high-sugar diets, for example, may shift bacterial diversity in ways that ripple through the virome (Boling et al., 2020). Conversely, diets rich in fiber and prebiotics promote bacterial diversity and are associated with more complex virome communities (De Jonge et al., 2022). Environmental factors also play a role, as exposure to different ecological niches, sanitation conditions, and microbial reservoirs influences the spectrum of viral colonization. Geographic differences in the virome have been observed, suggesting that cultural, dietary, and environmental variations contribute significantly to virome diversity at the population level.

Antibiotic use profoundly impacts virome composition. By disrupting bacterial hosts, antibiotics indirectly affect bacteriophage populations, often leading to blooms of temperate phages as they exit lysogeny in response to bacterial stress (Sutcliffe et al., 2021). This not only reshapes microbial communities but may also increase horizontal gene transfer, potentially spreading antibiotic resistance genes (Chen et al., 2022). The interplay between antibiotics, bacterial communities, and phages illustrates the delicate balance within the gut ecosystem and highlights the virome's central role in maintaining microbial stability under perturbation.

Beyond environmental influences, host genetics and immune responses also shape virome diversity. The immune system constantly surveils viral populations, influencing which viruses can persist and which are eliminated (Ezzatpour et al., 2023). Conversely, viral communities shape immune maturation and tolerance, establishing feedback loops that affect both microbial and host health (Santiago-Rodríguez & Hollister, 2022). Differences in host genetics may account for variability in virome composition between individuals, influencing susceptibility to infections, inflammatory conditions, and chronic diseases.

The virome's diversity is not merely a reflection of environmental noise but may hold functional significance for health. A more diverse virome may provide resilience against pathogenic invasions by stabilizing microbial communities, much like bacterial diversity protects against dysbiosis. On the other hand, disruptions or reductions in virome diversity have been associated with disease states such as inflammatory bowel disease, obesity, diabetes, and malnutrition (Cervantes-Echeverría et al., 2023). Whether these changes are causal or consequential remains a subject of ongoing investigation, but the correlations are strong enough to suggest that the virome plays an active role in shaping disease trajectories.

At the population level, the diversity of the gut virome reflects both commonalities and individuality. While certain viral families, such as Caudovirales bacteriophages, are consistently found across individuals, the specific strains and sequences vary greatly, forming what researchers describe as a "personalized virome." (Moreno-Gallego et al., 2019) This individuality may serve as a viral fingerprint, unique to each person yet influenced by shared environmental and cultural exposures. Such personalized viromes complicate efforts to define a universal healthy virome but also highlight the potential for precision medicine approaches that consider viral as well as bacterial microbiota.

Gut Virome and Immune System Modulation

The gut virome, an intricate collection of viruses inhabiting the human gastrointestinal tract, has emerged as a critical but underappreciated factor in shaping immunity. While bacteria and other microorganisms of the gut microbiome have long been recognized for their role in immune development and modulation, it is becoming increasingly clear that viruses, particularly bacteriophages and eukaryotic viruses, are equally important players in this dynamic ecosystem (Harper et al., 2021). The virome influences immunity at multiple levels, from the training and maturation of the immune system during early life to the regulation of inflammation and the orchestration of immune tolerance in adulthood (Beller & Matthijnssens, 2019). By interacting both directly with host cells and indirectly through their effects on bacterial populations, the gut virome modulates immune responses in ways that can determine health or predispose to disease.

From the earliest days of life, the virome begins to colonize the infant gut alongside bacteria. Bacteriophages arrive early and often mirror the bacterial populations they infect. This colonization is not a passive process but rather an essential driver of immune maturation (Shah et al., 2023). Viral exposure stimulates pattern recognition receptors such as toll-like receptors (TLRs) and RIG-I–like receptors, which detect viral nucleic acids and initiate signaling cascades (Takeuchi & Akira, 2010). These early signals help prime innate immunity, ensuring that the infant immune system learns to distinguish between harmless microbial residents and potential pathogens. Interestingly, studies have shown that infants raised in environments with reduced viral and microbial diversity may have altered immune development, supporting the notion that controlled viral exposure is crucial for establishing robust immunity (Khosravi & Mazmanian, 2013; Tabilas et al., 2022).

Bacteriophages exert powerful effects on immunity by shaping bacterial communities. Because phages regulate bacterial abundance and diversity, they indirectly control the microbial antigens and metabolites presented to the host immune system (Zuppi et al., 2022). This constant bacterial turnover driven by phages influences antigen presentation by dendritic cells and the education of T cells. Moreover, phages can mediate horizontal gene transfer, introducing new bacterial genes that alter surface molecules or metabolic products, which in turn modify immune responses (Chen et al., 2022). For example, bacterial production of short-chain fatty acids such as butyrate, which has anti-inflammatory effects, can be indirectly regulated by phage activity that affects butyrate-producing bacterial populations (Airola et al., 2023). Thus, phages serve as invisible conductors orchestrating a symphony of microbial signals that continuously shape host immunity.

Beyond indirect effects through bacteria, bacteriophages can interact directly with the immune system. Phages are capable of translocating across the intestinal epithelium and entering systemic circulation (Jonge et al., 2022). Once in contact with immune cells, they can stimulate cytokine release and modulate immune cell activity. Some studies have suggested that phages induce anti-inflammatory responses by promoting the release of interleukin-10, a cytokine that supports immune tolerance, while others indicate that phages can stimulate pro-inflammatory

pathways under certain conditions (Maciejewska et al., 2018). This dual potential highlights the context-dependent role of phages in immunity, where the same viral particles may promote tolerance in one setting and inflammation in another.

Eukaryotic viruses of the gut contribute a different dimension to immune modulation. Some, such as enteric adenoviruses or noroviruses, cause symptomatic infections, but even these interactions can leave lasting imprints on immune memory (Hitch et al., 2022). More intriguing, however, are findings that certain enteric viruses can serve beneficial roles. For instance, in germ-free or antibiotic-treated animals lacking bacterial microbiota, infection with murine norovirus has been shown to restore intestinal morphology and immune function to near-normal levels (Kernbauer et al., 2014). This suggests that viruses can substitute for bacterial signals in driving immune maturation, demonstrating a redundancy built into host-microbe interactions. Eukaryotic viruses may also provide low-level stimulation of innate immunity that maintains immune readiness without triggering overt disease, a phenomenon sometimes described as "training" or "priming" of the immune system.

The gut virome also interacts closely with the adaptive immune system. Viral antigens stimulate B cells to produce antibodies, including secretory IgA, which plays a key role in mucosal immunity (Desselberger, 2021). Antibodies not only neutralize pathogenic viruses but also shape viral ecology by selecting for certain phage or eukaryotic viral populations. The presence of antibodies in turn feeds back into viral diversity, as immune pressure forces viral adaptation through mutation and recombination (Dimitrov et al., 2023). This coevolutionary arms race between host immunity and the virome ensures a constant state of vigilance, where the immune system remains adaptable and responsive to new threats.

An important area of emerging research is the role of the gut virome in regulating inflammation. Chronic inflammatory conditions such as inflammatory bowel disease (IBD) have been linked to alterations in virome composition (Ezzatpour et al., 2023). In IBD patients, studies have found expansions of Caudovirales bacteriophages and reductions in viral diversity compared to healthy controls (Kåhrström, 2015). These changes are thought to exacerbate inflammation by disrupting bacterial communities and altering immune signaling. Conversely, a balanced virome may help maintain tolerance by promoting microbial stability and dampening excessive immune responses. Thus, the virome has a dual role: it maintains immune homeostasis through its equilibrium, but its disruption can lead the immune system towards pathology. For instance, murine norovirus has been shown to mitigate intestinal inflammation in models of chemically induced colitis and Citrobacter rodentium infection, demonstrating its capacity for protective effects (Bordon, 2014).

The virome's influence is not limited to local gut immunity but extends systemically. Viral particles, nucleic acids, and metabolites derived from viral-bacterial interactions can enter circulation and affect distant immune responses. For example, systemic exposure to viral components can modulate immune activity in the lungs, liver, or even the brain, contributing to the gut–immune–brain axis that links intestinal ecology to neurological and psychiatric health (Zhao et al., 2025). This systemic reach underscores the virome's role as a global regulator of immunity rather than a localized phenomenon.

The interplay between the virome and the immune system also has implications for susceptibility to infections and vaccines. Individuals with certain virome compositions may be more resistant to pathogenic infections because their immune systems are primed by ongoing viral exposures (Columpsi et al., 2016). Conversely, disruptions in virome diversity, whether due to antibiotics, poor diet, or environmental changes, may leave individuals more vulnerable to infections (Abeles et al., 2015). Vaccine responses can likewise be influenced by the virome, as preexisting viral exposures shape immune memory and responsiveness (Nishijima et al., 2022). Understanding these interactions could one day inform personalized vaccination strategies that take into account an individual's viral as well as bacterial microbiota.

One of the most fascinating aspects of virome-immune interactions is their evolutionary dimension. Humans and viruses have coexisted for millennia, and the immune system has evolved in constant dialogue with viral pressures (Clemente et al., 2012). Endogenous retroviruses, ancient viral sequences embedded within the human genome, are a testament to this long co-evolution (Wang et al., 2022). Some of these sequences play roles in regulating immune responses and even in fundamental processes such as placental development. The virome is thus not only a contemporary partner of the immune system but also a historical architect of its very structure and function.

Despite these insights, the study of the gut virome and immune modulation remains in its infancy. Many viral sequences remain unidentified, and the functional consequences of most viral-host interactions are poorly understood. Technical challenges, such as the difficulty of culturing viruses and the absence of universal viral markers, continue to slow progress. Nevertheless, advances in metagenomics, single-cell sequencing, and systems biology are beginning to illuminate the hidden world of viral-immune interactions. As knowledge expands, it is becoming increasingly apparent that the virome cannot be ignored in any comprehensive model of immune health.

Gut Virome in Health and Disease

The gut virome, composed of the full spectrum of viruses inhabiting the human gastrointestinal tract, is increasingly recognized as a central determinant of health and disease. While bacteria of the gut microbiome have been extensively studied, viruses, particularly bacteriophages, eukaryotic viruses, and endogenous retroviruses, were long regarded as marginal or simply parasitic (Cadwell, 2014). Today, research reveals that the virome is not merely a passive collection of viral elements but a dynamic, interactive community that exerts profound effects on microbial ecology, immune function, and overall host physiology (García et al., 2025). Its influence extends across the lifespan, shaping health trajectories from infancy to old age and contributing to both resilience and vulnerability in the face of disease. The study of the gut virome has become a frontier in microbiome science, with the potential to transform how we understand human health, prevent illness, and design therapies.

In a state of health, the gut virome functions as an integral component of microbial homeostasis. Bacteriophages, which dominate the virome numerically, play pivotal roles in regulat-

ing bacterial populations. By selectively infecting and lysing bacterial hosts, phages prevent unchecked bacterial overgrowth and maintain ecological balance (Kurilovich & Geva‐Zatorsky, 2025). This predator-prey dynamic is essential in sustaining bacterial diversity and preventing dysbiosis, which is associated with a range of chronic diseases (John et al., 2025). Moreover, phages contribute to horizontal gene transfer, serving as vectors of genetic material between bacteria. This process can promote bacterial adaptation, enabling the microbiota to better metabolize dietary substrates, resist environmental stressors, and produce metabolites that support host physiology (Wang et al., 2025). In this sense, bacteriophages act as unseen architects of the gut ecosystem, maintaining a delicate equilibrium that underpins health.

The virome's contributions to immunity are equally critical. From early life, viral exposures help educate the immune system, training it to differentiate between harmful and harmless signals. Bacteriophages influence bacterial antigen availability and thus indirectly shape immune recognition and tolerance (De Ora et al., 2025). Eukaryotic viruses, though less abundant, can provide signals that stimulate immune development, in some cases compensating for deficiencies in bacterial microbiota (Yang et al., 2025). Even endogenous retroviral sequences embedded in the human genome play roles in regulating immune gene expression and modulating inflammatory responses (Yang et al., 2025). Together, these elements of the virome create a dynamic dialogue with the immune system, fostering a balance between vigilance against pathogens and tolerance of commensals. A well-regulated virome thus contributes to immune homeostasis, reducing the risk of inappropriate inflammation or autoimmunity.

Beyond immunity, the virome supports metabolic and physiological processes. By shaping bacterial communities, phages influence the production of metabolites such as short-chain fatty acids, which are crucial for gut barrier integrity, energy metabolism, and anti-inflammatory signaling (Kumar et al., 2025). Viral activity also affects nutrient absorption and bile acid metabolism, indirectly influencing host energy balance and metabolic health (Jyoti & Dey, 2025). In this way, the virome contributes to functions that extend beyond the gut, impacting systemic physiology in subtle yet important ways.

However, the same properties that make the virome essential for health can also contribute to disease when balance is disrupted. Dysbiosis of the virome—characterized by altered viral diversity, expansions of certain viral families, or reductions in overall viral richness—has been linked to a wide range of conditions (Safarchi et al., 2025). One of the clearest associations is with inflammatory bowel disease. Studies consistently show that patients with Crohn's disease or ulcerative colitis exhibit increased abundance of Caudovirales bacteriophages and reduced overall virome diversity compared to healthy individuals (Saha & Hartmann, 2025). These changes may exacerbate inflammation by destabilizing bacterial communities and amplifying immune activation. The precise mechanisms remain under investigation, but it is increasingly clear that virome alterations are not simply byproducts of disease but active participants in its pathogenesis.

The virome is also implicated in metabolic disorders such as obesity and diabetes. Altered phage-bacteria interactions can shift bacterial composition in ways that promote energy harvest and fat storage. For example, changes in the abundance of phages targeting Bacteroidetes and Firmicutes may affect the balance of bacterial populations that metabolize dietary polysaccharides, thereby influencing caloric extraction (Higgins et al., 2021). Dysbiosis of the virome has been observed in obese individuals, with phage expansions correlated with metabolic dysfunction (Ahmed et al., 2024). These findings suggest that the virome contributes to metabolic health by maintaining bacterial communities that support balanced energy metabolism, and that disruption may predispose individuals to obesity and its complications.

Infections and immune-related conditions further highlight the virome's role in disease. Eukaryotic viruses in the gut can act as direct pathogens, causing gastroenteritis or systemic illness (Shabani et al., 2025). However, even non-pathogenic viral exposures may have consequences. Persistent or latent viral infections can modulate immune responses, sometimes providing protection against certain bacterial infections but also increasing susceptibility to autoimmunity or chronic inflammation (Lu & Wen, 2014). In some cases, viruses serve as environmental triggers for autoimmune diseases in genetically susceptible individuals, a relationship that underscores the virome's capacity to shape disease risk through complex interactions with the immune system (Garabatos & Santamaría, 2022).

Neurological and psychiatric conditions are another emerging domain where the virome may exert influence. The gut–brain axis, long known to link microbial activity with brain function, may include viral contributions as well. By modulating bacterial communities and immune responses, the virome may influence neuroinflammation and neurotransmitter metabolism (Generoso et al., 2020). Preliminary evidence suggests associations between virome alterations and conditions such as autism spectrum disorders and depression, though causal mechanisms remain speculative (Wang & Kasper, 2013). Still, the possibility that viruses in the gut can indirectly shape mental health presents fresh prospects for research into the microbiota–gut–brain connection.

The virome's role in cancer is similarly complex. On one hand, viruses are established oncogenic agents, with certain human papillomaviruses and Epstein-Barr virus providing well-known examples (Yaqub et al., 2025). In the gut, chronic viral stimulation of the immune system or disruption of microbial communities may create pro-inflammatory environments that promote tumorigenesis (Porta et al., 2010). On the other hand, bacteriophages may exert protective effects by maintaining bacterial balance and limiting pathogenic overgrowth that could contribute to carcinogenesis (Yamashina et al., 2022). Some phages are even being investigated as therapeutic agents to selectively target pathogenic bacteria associated with colorectal cancer (Liping et al., 2024). Thus, the virome may both contribute to and protect against cancer, depending on context and composition.

Therapeutically, the virome presents opportunities as well as challenges. Phage therapy, once overshadowed by antibiotics, is regaining attention as a precision tool to target bacterial pathogens without disrupting beneficial microbiota (Ooi & Yeh,

2024). By selectively modulating bacterial populations, phages could restore microbial balance in conditions such as inflammatory bowel disease or Clostridioides difficile infection. Beyond bacteriophages, researchers deliberately use non-pathogenic eukaryotic viruses to stimulate immune responses or support microbiota function, marking a novel therapeutic frontier (Marongiu et al., 2021). However, manipulating the virome also carries risks, given the potential for unintended immune activation or horizontal gene transfer. Prior to the widespread implementation of such strategies, a deeper understanding of virome ecology and host interactions will be essential.

From a population health perspective, the virome is also relevant to resilience against emerging infectious diseases. Viral communities may provide ecological buffering by limiting colonization by pathogens through competitive interactions or by stimulating baseline immune readiness (Carroll et al., 2018). At the same time, disruptions of the virome—whether through antibiotics, poor diet, or environmental changes—may weaken this resilience, leaving populations more vulnerable to outbreaks (B ćh et al., 2022). The virome thus represents not only an individual-level determinant of health but also a collective one, shaping how populations respond to infectious and chronic diseases alike.

Despite growing recognition of its importance, much of the gut virome remains uncharacterized. The vast majority of viral sequences identified in metagenomic studies cannot be assigned to known taxa, forming what researchers call the "viral dark matter." (Beller & Matthijnssens, 2019) This knowledge gap reflects both the enormous diversity of viral genomes and the technical limitations of current sequencing and computational methods. Unlike bacteria, viruses lack universal genetic markers that facilitate classification, making it far more difficult to map their diversity (Abrescia et al., 2012). As a result, our understanding of virome composition and function is still in its infancy, and much of its contribution to health and disease likely remains hidden.

Advances in sequencing technologies and bioinformatics are beginning to illuminate this dark matter. Novel viral families are being discovered, and viral databases are expanding rapidly (Ogilvie & Jones, 2015). Integrative approaches that combine viral, bacterial, metabolomic, and immunological data hold promise for unraveling the complex networks linking the virome to health outcomes (Pargin et al., 2023). As this field matures, the virome may prove to be as central to microbiome science as bacteria, reshaping our understanding of what constitutes a healthy microbiome and redefining strategies for maintaining health.

The recognition of the gut virome's role in both health and disease carries profound implications. It reframes viruses not only as pathogens but also as symbionts and ecological regulators. It highlights the importance of viral diversity as a marker of resilience and stability. It suggests that interventions targeting the virome could provide new tools for preventing and treating disease. And it emphasizes that human health cannot be fully understood without considering the viral dimension of the microbiome.

Ultimately, the gut virome embodies the paradox of viruses: destructive in some contexts, indispensable in others. It represents both a threat and a safeguard, a driver of disease and a guardian of balance. In health, it maintains microbial equilibrium, educates the immune system, and supports metabolic functions. In disease, its disruption contributes to inflammation, metabolic dysfunction, autoimmunity, neurological disorders, and cancer. The challenge for science is to disentangle these opposing roles and harness the virome's potential for therapeutic benefit.

As the study of the virome advances, it may transform medicine in ways analogous to the bacterial microbiome revolution. Understanding and manipulating the viral dimension of the gut could lead to precision therapies that restore balance, vaccines that leverage viral diversity, and preventive strategies that strengthen resilience at both individual and population levels (Kurilovich & Geva‐Zatorsky, 2025). The gut virome, once invisible and ignored, is now emerging as a central axis of health and disease, with the power to redefine the boundaries of microbiology, immunology, and medicine.

Conclusion

The gut virome, long overlooked in microbiome research, has emerged as a vital determinant of both individual and population health. Comprising bacteriophages, eukaryotic viruses, and endogenous viral elements, the virome exerts multifaceted influences that extend far beyond the intestinal lumen. Its contributions to microbial homeostasis, immune modulation, metabolic function, and disease resilience highlight its central role in maintaining systemic health. By regulating bacterial populations, bacteriophages maintain ecological balance within the gut, prevent overgrowth of pathogenic species, and facilitate genetic exchange that promotes adaptive capacity in the microbiota. These interactions underpin not only digestive and metabolic homeostasis but also the immune system's ability to distinguish between commensal and pathogenic signals. Eukaryotic viruses, while often pathogenic, also play subtler roles in shaping immune responses, stimulating mucosal immunity, and potentially compensating for deficiencies in bacterial signals. Together, these viral communities create a dynamic ecosystem that sustains health across the lifespan.

Disruptions to the gut virome, whether through antibiotics, diet, environmental exposures, or disease, can destabilize microbial networks and increase susceptibility to a wide spectrum of conditions. Inflammatory bowel disease, metabolic disorders such as obesity and diabetes, neurological and psychiatric conditions, and even cancer have all been associated with alterations in virome composition and diversity. These findings underscore the virome's dual nature: it is simultaneously a guardian of health and a potential contributor to pathology when equilibrium is lost. At the population level, a balanced virome enhances resilience to infectious agents, supports immune development, and stabilizes microbial ecosystems, whereas widespread disruption may increase the burden of disease across communities.

Despite these insights, much of the virome remains uncharacterized, and the vast "viral dark matter" represents a frontier in medical and ecological research. Advances in metagenomics, bioinformatics, and systems biology are beginning to illuminate this hidden world, revealing new viral fami-

lies, interactions, and functional roles. Understanding the gut virome is not only critical for comprehending human biology but also for designing preventive strategies, therapeutic interventions, and public health policies that leverage viral ecology to promote population well-being. Recognizing the virome as an integral component of health transforms our perspective, emphasizing that human well-being is inseparable from the invisible viral networks that coevolve within us. In this sense, the gut virome emerges as both a window into the complexities of human physiology and a promising target for interventions aimed at sustaining health and preventing disease on a global scale.■

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