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Review

Precision Immunonutrition and Gut Virome Modulation in Early Life: A Multi-Omic Framework for Pediatric Autoimmunity Prevention

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Abstract

Background/Objectives: The chronological assembly of the gut virome during early life occurs in close coordination with bacterial colonization and is thought to influence mucosal immune maturation. While genetic susceptibility creates a clear predisposition for early-onset pediatric autoimmune conditions, maternal and infant dietary factors represent potentially modifiable environmental modulators of this evolving viral–bacterial ecosystem. This narrative review evaluates early-life pediatric autoimmunity through a mechanistically driven immunonutritional framework spanning the neonatal period through early childhood. **Methods:** Based on targeted literature searches of PubMed/MEDLINE, Scopus, and Web of Science (January 2000–October 2026), this manuscript synthesizes observational birth-cohort data and experimental multi-omic findings—integrating viromic profiling, targeted metabolomics, and peripheral blood transcriptomics—to propose an exploratory biomarker and research surveillance framework. **Results:** We evaluate preclinical and observational evidence regarding the capacity of specific human milk oligosaccharides (HMOs) to act as soluble structural decoys against selected enteric viruses (primarily norovirus and rotavirus strains) and to support epithelial barrier integrity. Furthermore, we examine how micronutrients and structured lipids—specifically vitamin D3, long-chain polyunsaturated fatty acids (LC-PUFAs), and dietary polyphenols—modulate epithelial membrane organization, mucosal redox balance, and immune signaling in experimental models, while highlighting current gaps in direct clinical evidence regarding antiviral sensing and interferon modulation in human infants. Finally, we discuss the hypothesis that maternal and infant dietary fiber networks support short-chain fatty acid (SCFA) availability to help maintain mucosal anaerobiosis and favor temperate bacteriophage dynamics. **Conclusions:** Establishing a structured,

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multi-omic research surveillance timeline across early life offers an exploratory, non-invasive conceptual strategy. Pending analytical standardization and validation in prospective longitudinal trials, this framework may help guide future precision immunonutrition studies aimed at supporting peripheral self-tolerance and mitigating pediatric autoimmune risk.

Keywords: human milk oligosaccharides; neonatal nutrition; gut virome; maternal-fetal conduit; type 1 diabetes; celiac disease; short-chain fatty acids; immunomodulation; precision nutrition

1. Introduction

The neonatal period, encompassing the first 28 days of extrauterine life, initiates a critical developmental continuum extending through infancy and early childhood (the first two to three years of life) for immune priming and metabolic programming. While classical early-life research has characterized the role of the pioneering bacterial microbiome, recent high-throughput viromic sequencing has uncovered a dense and dynamic viral ecosystem within the developing intestine, termed the early-life gut virome [1]. This microenvironment is predominantly composed of prokaryotic bacteriophages alongside opportunistic eukaryotic viruses, expanding rapidly after birth [2,3]. In healthy infants, these viral populations are considered potential ecological regulators that interact with bacterial communities and accompany the functional maturation of the immature mucosal barrier [1,4].

When this delicate viral equilibrium is disrupted by sub-optimal early dietary choices, a state of intestinal dysbiosis may emerge within the first weeks of life [2]. Preclinical and observational data suggest that such viral–bacterial imbalances can compromise the structural integrity of the single-cell epithelial sheet, potentially disrupting tight junction protein networks and increasing paracellular permeability—a state clinically described as a "leaky gut" [3,4]. Hypothetically, this structural breakdown could facilitate the translocation of luminal antigens, viral particles, and endotoxins into the sub-epithelial space, triggering chronic pro-inflammatory signaling cascades that may impair peripheral self-tolerance and contribute to systemic autoimmune pathologies [1,2,4,5].

Pediatric autoimmune disorders, most notably Type 1 Diabetes Mellitus (T1DM) and Celiac Disease (CD), arise from a complex interaction between a distinct genetic predisposition and early environmental triggers [6–8]. Genetic screening routines regularly identify high-risk human leukocyte antigen (HLA) genotypes, specifically HLA-DR4-DQB1*0302 and/or DR3-DQB1*0201 for T1DM, and HLA-DQ2 or HLA-DQ8 for CD, which are established genetic determinants [6,9]. However, epidemiological evidence indicates that genetic susceptibility alone is insufficient to drive clinical disease; concordance rates for T1DM in monozygotic twins remain below 50%, and these risk alleles are carried by a large percentage of healthy individuals who never exhibit clinical symptoms [7,8].

This clinical gap highlights the potential contribution of early environmental triggers, with persistent enteric viral colonization during infancy and early childhood investigated as a primary suspect [10,11]. Experimental and longitudinal cohort studies suggest that when opportunistic viruses, such as enteroviruses or rotaviruses, colonize the immature gut, they may contribute to mucosal injury [12–14]. In genetically vulnerable individuals, persistent viral replication has been associated with a chronic tissue-level interferon gene signature, characterized by the sustained activation of Type I Interferon (IFN-α and IFN-β) pathways [15–17]. This pro-inflammatory environment is hypothesized to promote

cellular stress, apoptosis, and self-antigen presentation by mucosal dendritic cells, potentially facilitating early autoantibody seroconversion—though direct causal pathways in human neonates remain under investigation [18–20].

While environmental viral exposures have historically been viewed as unpredictable, nutritional immunology offers a promising theoretical framework for early clinical intervention starting in the neonatal window [21]. The early-life dietary matrix supplies bioactive compounds that interact with the intestinal lining and may help modulate host–virus interactions before extensive tissue damage occurs [22,23]. This review evaluates the role of early-life nutrition through a mechanistically driven framework integrating current observations of gut virome development, intestinal barrier function, and immune regulation [15].

Specifically, we examine experimental evidence suggesting that human milk oligosaccharides (HMOs) can act as soluble anti-viral structural analogs against selected viral strains and support epithelial barrier development. We also evaluate how critical nutrients, such as Vitamin D and long-chain polyunsaturated fatty acids (LC-PUFAs), may influence host enterocyte membranes and tissue-level inflammatory signaling in experimental models. Finally, we discuss the hypothesis that fiber-derived short-chain fatty acids (SCFAs), mediated through maternal and early-life diet networks, influence bacteriome–phage dynamics to favor lysogeny and support the intestinal barrier. Whereas previous narrative syntheses have focused primarily on the descriptive pathophysiology linking early-life gut virome perturbations to autoimmune pathogenesis, the present manuscript extends the field by critically appraising the translational evidence for targeted immunonutritional modulators and outlining an exploratory multi-omic research roadmap from the neonatal window through early childhood.

To ensure developmental precision across the studies discussed herein, the neonatal period strictly refers to the first 28 days of extrauterine life, early infancy encompasses 1 to 6 months of age, late infancy spans 6 to 12 months, and early life (or early childhood) is used as an overarching term covering the continuum from birth through the first two to three years of life, reflecting distinct stages of gut barrier maturation, feeding transitions, and virome assembly.

2. Literature Search Methodology

2.1. Literature Search Strategy

To construct this narrative review, targeted literature searches were conducted across PubMed/MEDLINE, Scopus, and Web of Science covering peer-reviewed articles published in English from January 2000 through October 2026, with priority given to seminal mechanistic studies and recent multi-omic clinical cohorts published within the past decade. Rather than relying on a single restrictive query, we performed iterative, topic-specific searches combining Medical Subject Headings (MeSH) and free-text terms across three core thematic domains: (i) early-life virome and pediatric autoimmunity (“neonatal gut virome” OR “infant virome” OR “phageome” OR “bacteriophages” OR “enterovirus” combined with “pediatric autoimmunity” OR “type 1 diabetes” OR “celiac disease” OR “islet autoimmunity”); (ii) mucosal barrier and innate viral sensing (“intestinal epithelial barrier” OR “tight junctions” OR “prophage induction” OR “type I interferon”); and (iii) targeted nutritional modulators (“human milk oligosaccharides” OR “vitamin D” OR “omega-3 polyunsaturated fatty acids” OR “arachidonic acid” OR “short-chain fatty acids” OR “dietary fiber” OR “polyphenols”).

2.2. Study Selection Criteria and Evidence Appraisal

Because this work was designed as a narrative mechanistic synthesis rather than a systematic review, formal PRISMA record counts and quantitative meta-analyses were not performed. Instead, we prioritized original longitudinal birth cohort studies, randomized controlled trials, metagenomic and viromic analyses, and foundational in vitro or in vivo mechanistic studies investigating early-life virome assembly, intestinal epithelial barrier integrity, and nutritional immunomodulation. Non-peer-reviewed preprints, conference abstracts, case reports, and studies lacking relevance to early-life mucosal immunity were excluded. During synthesis, findings were qualitatively appraised and stratified according to evidence tier—explicitly distinguishing observational human cohort correlations and preclinical cellular or animal data from unvalidated clinical hypotheses. Reference lists of key primary articles and consensus guidelines were also manually screened to identify additional relevant publications.

3. Stepwise Assembly of the Early-Life Virome and Nutritional Anchors

3.1. The Chronological Succession of the Neonatal Phageome and Ecological Convergence

The colonization and structural development of the gut virome follow a strict age-dependent pattern of ecological succession that initiates immediately after birth [22]. Deep viromic sequencing of pioneer neonatal meconium and first-week stool specimens has reported a relatively low abundance or limited detection of eukaryotic viral sequences during the first days of life, although findings may vary depending on sampling and sequencing methodologies [22,24–26]. However, within the first days of extrauterine life, a rapid colonization event takes place [27]. This initial neonatal stabilization is heavily dominated by prokaryotic viruses, specifically non-enveloped DNA bacteriophages belonging to the *Caudoviricetes* class and the *Microviridae* family [22,27]. Longitudinal studies of early-life viromes show that viral richness increases significantly over the first weeks of life, accompanied by predictable shifts in community structure [22,26,27].

Interestingly, the primary reservoir for these baseline phages does not originate from the immediate postnatal environment. Instead, a vast majority of these early sequences arise from the induction of temperate prophages residing natively within the chromosomes of pioneering maternal bacteria that seed the newborn. These pioneer strains, including facultative anaerobes such as *Proteobacteria* (e.g., *Enterobacteriaceae*) alongside early obligate anaerobes such as *Bifidobacterium* species and anaerobic *Firmicutes*, act as the initial cellular hosts in the neonatal gut [22,26,27]. Temperate prophages carried by pioneering bacterial colonizers may undergo induction and enter the lytic cycle, thereby contributing to the establishment of the neonatal phageome. Metabolic and dietary transitions, as well as oxidative stress, represent biologically plausible triggers of prophage induction. However, the direct contributions of maternal antibodies and intestinal oxygen gradients remain largely inferential, while intrinsic phage–host dynamics appear relatively resilient to a range of environmental influences [22,27]. As the neonate transitions into early infancy, phageome profiling demonstrates a clear progression, showing a relative decrease in the abundance of bacteriophages and an increase in eukaryotic families like *Anelloviridae* [28,29]. Phage-encoded auxiliary metabolic genes (AMGs) actively shift during this succession, showing specific enrichment in metabolic pathways that support dietary transitions as the child moves from an exclusive milk diet to complex polysaccharides [30]. The temporal succession of the early-life gut virome, together with the age-dependent contributions of maternal, perinatal, and nutritional factors, is summarized in Figure 1.

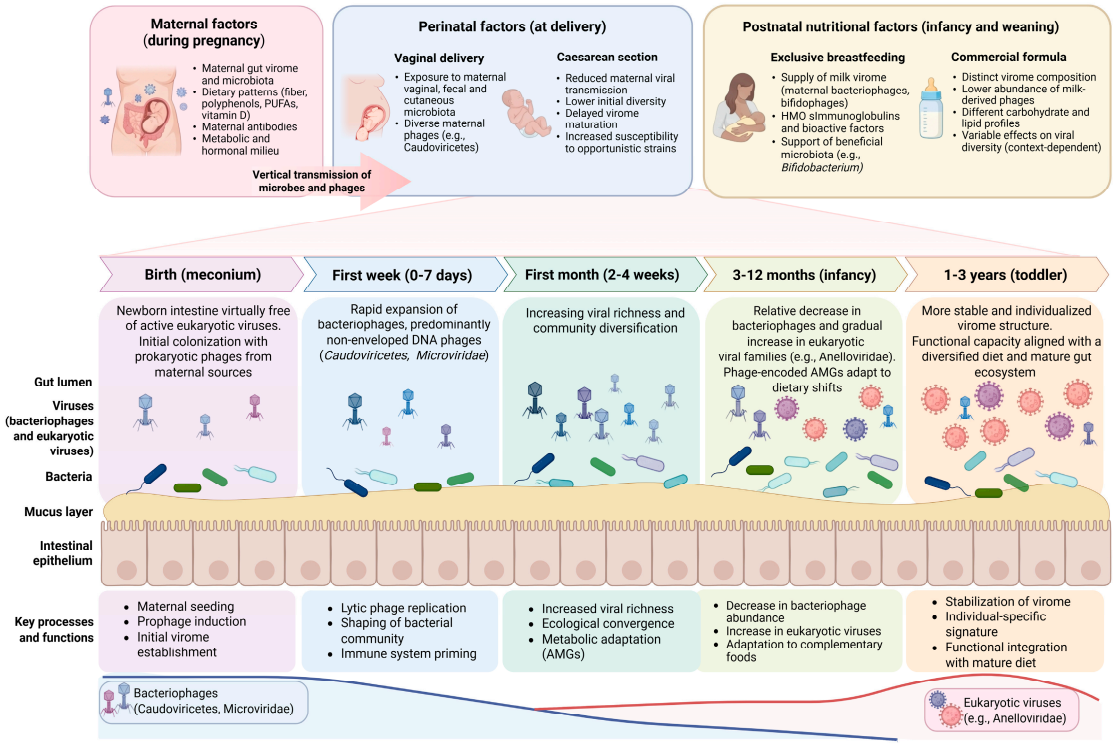


Figure 1. Temporal Dynamics of Early-Life Gut Virome Succession: Maternal, Perinatal, and Nutritional Determinants. *Abbreviations:* AMGs, auxiliary metabolic genes; HMOs, human milk oligosaccharides; PUFAs, polyunsaturated fatty acids. Created in BioRender. Fortis, S. (2026).

3.2. Vertical Maternal Seeding and the Impact of Birth Delivery Modes

The baseline architecture of the neonatal phageome is heavily dictated by vertical maternal inheritance during delivery [31]. Neonates delivered via the vaginal canal undergo standard vertical seeding with maternal vaginal, fecal, and cutaneous microbes [31,32]. This direct exposure establishes a highly diverse and stable phage infrastructure characterized by temperate *Caudoviricetes* that co-evolve harmoniously with permanent, long-term bacterial colonizers such as *Bacteroides* species [22,32]. These vertically transmitted phage strains are highly individual-specific and demonstrate significant temporal stability, forming a personal persistent mobilome [33].

Conversely, neonates delivered via Caesarean section experience a profound disruption in this maternal inheritance cascade. C-section delivery removes the immediate contact with the maternal vaginal fluid and intestinal microflora, causing a major alteration that delays the normal maturation of the phage community [31]. Available evidence suggests that Caesarean delivery may be associated with differences in early-life viral community composition and maternal phage transmission, although the magnitude and persistence of these differences remain incompletely characterized [22,31]. However, this delay opens a temporary window of susceptibility during the first month of life, allowing for the colonization and overgrowth of atypical, opportunistic, or environmental strains [21,29]. Nevertheless, their direct clinical implications for neonatal susceptibility to infection or later immune-mediated diseases require further investigation.

3.3. Exclusive Breastfeeding vs. Commercial Formula Trajectories

Following the immediate postnatal period, infant feeding practices represent an important modifiable determinant of early-life gut virome development, although their relative contribution varies with postnatal age. Large-scale metagenomic analyses indicate that the mode of delivery and gestational age exert a more significant influence on the

composition of the gut virome during the early stages of life, whereas the contribution of the feeding method becomes increasingly pronounced throughout infancy (after approximately the 3rd month). Consequently, feeding represents an important modifiable factor, though it is not the most potent external factor at all ages [34].

Feeding effectively serves as a continuous, daily viral and nutritional infusion into the newborn's gastrointestinal tract. Human breast milk contains a highly complex, non-pathogenic virome composed of maternal bacteriophages and protective bifidophages that are vertically transferred to the newborn during suckling [22,27]. Breast milk contains diverse viral communities, including bacteriophages, which may contribute to the maternal-infant transmission of viruses and the initial shaping of the gut virome. However, the extent to which bacteriophages derived from breast milk become established and persist long-term in the infant's gut has not been fully elucidated [34,35].

Shotgun sequencing profiles confirm that exclusively breastfed neonates maintain an intestinal viral structure that closely mirrors the maternal milk communities, reinforcing a balanced, non-inflammatory mucosal environment [22].

Conversely, formula-fed infants may follow an altered developmental trajectory, which has been discussed in the context of early intestinal mucosal vulnerability and necrotizing enterocolitis [36]. In longitudinal cohort profiling, Liang et al. described a stepwise assembly of the infant gut virome in which human-cell-infecting eukaryotic viruses gradually accumulate during the first four months of life, with exclusively formula-fed infants showing higher eukaryotic viral loads than breastfed infants [22].

The study revealed that breastfeeding is associated with a reduced accumulation of potentially pathogenic eukaryotic viruses compared to exclusive formula feeding. Maternal antibodies, HMOs, lactoferrin, and other bioactive components are potential mechanisms contributing to this association, although the specific contribution of each has not yet been fully elucidated. Importantly, these findings do not establish that formula feeding directly induces pathogenic viral replication or intestinal inflammation.

However, findings regarding the association between infant feeding methods and gut virome diversity remain inconsistent across studies. Zeng et al., as well as Garmaeva et al., reported higher viral richness or higher indices of viral diversity in formula-fed infants, whereas Pan et al. observed greater gut virome diversity in breastfed infants at six months of age [34,35,37].

These divergent findings may reflect differences in the age of the infants, the characteristics of the populations studied, the methodological approaches used to analyze the virome, and the specific viral populations examined. It is important to note that higher viral diversity does not necessarily indicate intestinal dysbiosis or adverse clinical outcomes. Rather, increases in viral richness often reflect physiological ecological maturation, and their biological interpretation depends critically on taxonomic composition (e.g., commensal bacteriophages versus opportunistic eukaryotic viruses), functional activity, host–virus interactions, and infant developmental stage, as well as major confounding variables including delivery mode, feeding practices, perinatal or infant antibiotic exposure, and maternal microbiota composition. Garmaeva et al. reported an association between formula feeding and increased induction of prophages associated with bacteria of the genus Bacteroides, including *Bacteroides fragilis*. This association persisted even after statistical adjustment for the abundance of the bacterial host. This finding suggests that dietary exposures may influence bacteriophage dynamics, rather than solely the composition or abundance of bacterial populations. The absence of maternal immunoglobulins, lactoferrin, and complex milk glycans natively present in human colostrum and mature milk removes key luminal factors that normally help restrict eukaryotic viral attachment and replication [22,28]. Consequently, opportunistic viral families are observed at higher relative abundances in the formula-fed gut lumen during early infancy [29]. In experimental

models, unbuffered eukaryotic viral expansion can exert immunogenic stress on the immature gut-associated lymphoid tissue (GALT) and interact directly with the single-cell epithelial sheet, potentially promoting low-grade mucosal inflammation and altering local immune homeostatic thresholds [10,15,38,39]. While these mechanistic interactions offer a biologically plausible explanation for the protective associations observed with breastfeeding, longitudinal human studies are still required to confirm whether formula-associated virome trajectories directly prime the neonatal mucosal compartment for early autoimmune responses [11,14]. Overall, these findings suggest that the mode of infant feeding influences the longitudinal development of the gut virome through multiple, potentially interconnected mechanisms, including maternal viral transmission, interactions between bacteriophages and bacterial hosts, and the regulation of eukaryotic viral communities.

However, it remains unclear to what extent these variations in the composition and dynamics of the gut virome translate into alterations in intestinal barrier function, the maturation of the mucosal immune system, or future predisposition to the development of autoimmune diseases. Further longitudinal and mechanistic studies are required to clarify the clinical significance of the observed associations.

3.4. Molecular Mechanisms of HMOs as Soluble Anti-Viral Decoys

The protective antiviral and immunomodulatory effects of breast milk may be partly mediated by HMOs, a highly specialized group of unconjugated glycans that can act through multiple mechanisms, including their potential function as soluble decoy receptors [22]. Synthesized within the mammary gland, HMOs constitute a major solid component of human milk, averaging a concentration of 5 to 20 g/L [40]. Structurally, these complex carbohydrates are composed of five core monosaccharides: D-glucose, D-galactose, *N*-acetylglucosamine, L-fucose, and sialic acid [23,40]. The specific structural linkages divide them into major functional categories: fucosylated HMOs (e.g., 2′-fucosyllactose [2′-FL]), sialylated HMOs (e.g., 3′-sialyllactose [3′-SL]), and neutral non-fucosylated core HMOs (e.g., Lacto-*N*-neotetraose [LNnT]) [40].

While a portion of these complex sugars serves as metabolic prebiotics that fuel beneficial pioneer bacteria, HMOs are largely resistant to digestion by host enzymes, allowing substantial amounts to reach the intestinal lumen without being degraded. Here, specific HMO structures exert a highly sophisticated defense function, operating as soluble structural analogs or antiviral decoys [40]. Certain enteric viruses, including specific rotavirus strains, recognize host–cell surface glycans, such as histo-blood group antigens (HBGAs) or sialic acid-containing structures, during viral attachment. However, receptor usage varies considerably across viral species and strains [12,15,39]. This cellular attachment is an absolute requirement for viral endocytosis, intracellular replication, and eventual host cell lysis [39].

Structurally distinct HMO classes exert differential, strain-specific effects on host–virus interactions rather than uniform broad-spectrum antiviral activity. HMOs present structural similarities to certain fucosylated and sialylated glycan epitopes expressed on host-cell surfaces, potentially enabling them to interfere with specific virus–host interactions. Specifically, fucosylated HMOs such as 2′-FL mimic α1,2-fucosylated histo-blood group antigens (HBGAs) targeted by specific norovirus and rotavirus genotypes, whereas sialylated HMOs such as 3′-SL and 6′-SL resemble sialic acid-containing glycans recognized by sialic-acid-dependent viruses; conversely, neutral non-fucosylated core structures like LNnT act primarily as selective metabolic substrates rather than high-affinity viral decoys. Free-floating viral particles entering the gut lumen may bind to these soluble dietary HMO decoys instead of host enterocytes. For instance, fucosylated structures like 2′-FL may modulate interactions between certain enteric viruses and host cells, although

their effects are virus- and strain-dependent and do not necessarily involve competitive inhibition of viral attachment [12,15,22,23,40]. The study by Ramani et al. found that HMOs did not act as decoy receptors for the specific neonatal rotavirus strain G10P—and in some experimental contexts even enhanced its infectivity [41]. Therefore, we cannot generalize the mechanism of 2′-FL to all rotaviruses or enteroviruses [41].

This competitive trapping mechanism may interfere with the attachment of susceptible viral strains to intestinal epithelial cells, potentially reducing viral entry and infectivity. However, evaluating the protective potential of HMOs requires clearly distinguishing such direct luminal antiviral interference from three complementary indirect pathways: (i) microbiota-mediated effects, whereby neutral core and fucosylated HMOs selectively promote *Bifidobacterium*-dominated communities and SCFA production that competitively restrict opportunistic pathogens; (ii) direct epithelial barrier maturation, whereby HMOs regulate enterocyte differentiation and tight junction-associated proteins—including claudins, occludin, and zonula occludens-1 (ZO-1)—independently of viral trapping [22,39,42]; and (iii) direct immunomodulation, whereby specific HMOs interact with host glycan-binding receptors (such as galectins, siglecs, and C-type lectins) on mucosal epithelial and immune cells to modulate mucosal cytokine signaling. Importantly, while soluble decoy activity has been demonstrated experimentally against specific norovirus and rotavirus strains—and autoimmunity-specific protection by HMOs has thus far been reported primarily in preclinical non-obese diabetic (NOD) mouse models—direct experimental evidence that HMOs inhibit the attachment or replication of the specific enterovirus species implicated in human T1DM or CD remains lacking [10,12,15,17,41,43]. However, whether these effects influence persistent type I interferon signaling or subsequent autoantibody seroconversion remains to be established. The influence of delivery mode and infant feeding on early-life gut virome composition, together with the proposed antiviral mechanisms of HMOs, is schematically illustrated in Figure 2.

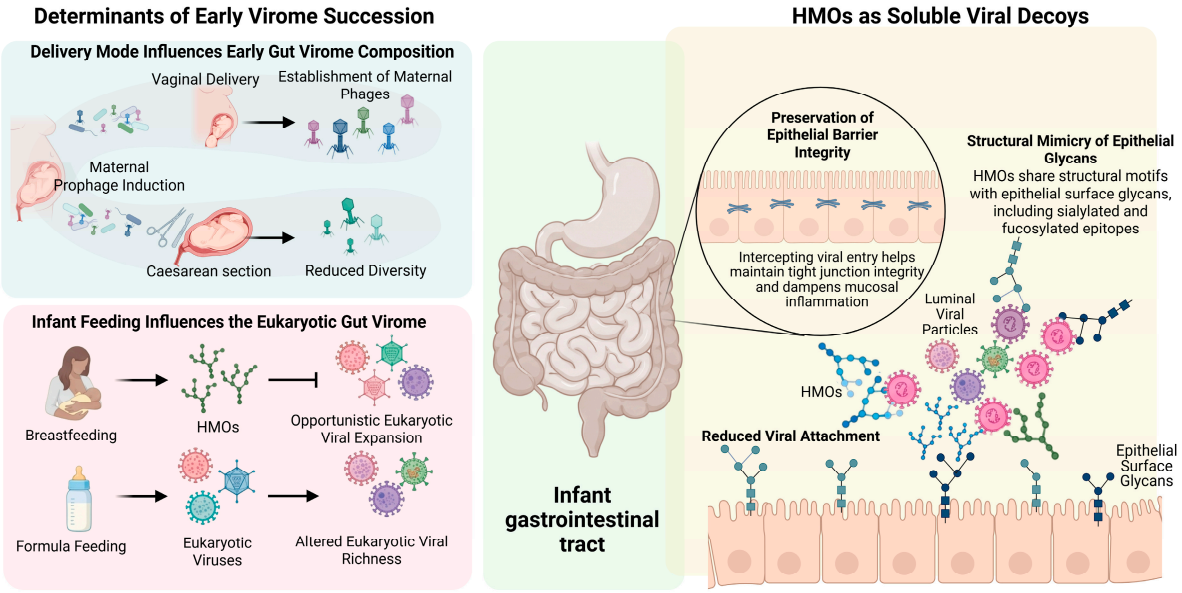


Figure 2. Determinants of Early-Life Gut Virome Composition. Schematic representation of the influence of delivery mode and infant feeding practices on early-life gut virome composition, alongside the proposed antiviral mechanisms of human milk oligosaccharides (HMOs) as soluble receptor decoys (demonstrated experimentally for selected norovirus and rotavirus strains, whereas direct inhibition of diabetogenic enteroviruses remains unproven). Created in BioRender. Fortis, S. (2026).

4. Micronutrients and PUFAs as Proposed Neonatal Mucosal Stabilizers

4.1. Cholecalciferol (Vitamin D3) and the Epigenetic Modulation of Neonatal Barrier Tolerance

Dietary and micro-nutritional factors serve as important environmental signals that may influence the structural development and functional baseline of the intestinal barrier during the strict neonatal period (the first 28 days of life) [6–8]. Among these, Vitamin D3 (cholecalciferol) has been investigated for its potential role in supporting mucosal tissue homeostasis and immune tolerance after birth [6]. In genetically susceptible neonates, early postnatal exposure to enteric viral pathogens may induce local tissue stress and contribute to a chronic pro-inflammatory state. This early process has been associated with a persistent interferon gene signature, characterized by sustained activation of Type I Interferon pathways, which have been implicated in the pathogenesis of T1DM and potentially CD, although their direct contribution to subsequent autoantibody seroconversion remains uncertain [16,17,20].

To ensure adequate neonatal vitamin D status and prevent vitamin D deficiency, oral cholecalciferol supplementation is typically recommended at 400 IU/day for term infants, whereas preterm neonates, critically ill newborns, and infants at increased risk of vitamin D deficiency may require individualized supplementation based on gestational age, body weight, nutritional intake, underlying clinical conditions, and biochemical findings [44]. In selected high-risk neonates, total daily vitamin D intake may reach up to 1000 IU/day when clinically indicated, in accordance with population-specific nutritional guidelines and under appropriate biochemical monitoring [44]. Supplementation aims to maintain adequate circulating 25-hydroxyvitamin D [25(OH)D] concentrations, with levels of at least 20 ng/mL (50 nmol/L) generally considered indicative of vitamin D sufficiency for skeletal health [44].

Although higher serum 25(OH)D concentrations, including the range of 40–60 ng/mL, have been discussed in adult and general observational literature in relation to potential extra-skeletal and immunomodulatory benefits—particularly the maintenance of intestinal mucosal homeostasis and immune barrier function—no specific therapeutic threshold has been established in randomized clinical trials to support neonatal mucosal defense, prevent virus-associated inflammation, or reduce the risk of pediatric autoimmunity [6,45–51]. At the sub-cellular level within gut tissues, active 1,25-dihydroxyvitamin D3 (calcitriol) binds to the intracellular Vitamin D Receptor (VDR), which regulates the transcription of genes involved in epithelial barrier function and immune responses [47]. Calcitriol–VDR signaling appears to modulate innate immune sensing and inflammatory pathways in a cell- and stimulus-dependent manner, rather than uniformly suppressing antiviral responses [52–54].

Although experimental studies have demonstrated anti-inflammatory effects under specific conditions, there is currently insufficient evidence that neonatal vitamin D supplementation attenuates viral nucleic acid sensing or persistent type I interferon signaling within pancreatic islets or mesenteric lymph nodes [17,52,53,55,56]. At the same time, VDR signaling may influence the differentiation and function of regulatory T cells and the production of anti-inflammatory cytokines, potentially contributing to mucosal immune homeostasis. However, whether these immunomodulatory mechanisms prevent neonatal intestinal injury or subsequent autoimmune seroconversion in humans remains to be established [6,45,53].

4.2. Omega-3 PUFAs and Neonatal Cellular Membrane Optimization

Postnatal dietary interventions may influence neonatal cellular membrane composition and immune signaling through the provision of long-chain PUFAs (LC-PUFAs) [57]. In preterm infants, nutritional recommendations emphasize adequate provision of

docosahexaenoic acid (DHA; 30–65 mg/kg/day) together with arachidonic acid (ARA; 30–100 mg/kg/day), maintaining an ARA-to-DHA ratio of 0.5–2 and limiting eicosapentaenoic acid (EPA) intake to less than 20 mg/kg/day, in accordance with ESPGHAN recommendations [44]. These fatty acids contribute to membrane development and physiological cellular functions during a period of rapid tissue growth and maturation. Importantly, ARA is not merely a pro-inflammatory omega-6 fatty acid to be displaced by omega-3 supplementation; rather, both ARA and DHA are essential structural and functional components of developing tissues—although evidence derived from preterm infants (where fatty acid accretion deficits and necrotizing enterocolitis risks are heightened) cannot be directly extrapolated to term neonates carrying genetic susceptibility to autoimmunity [44,58].

Observational evidence from the Diabetes Autoimmunity Study in the Young (DAISY) further suggests a potential association between omega-3 PUFA exposure and subsequent autoimmune risk. In children genetically predisposed to T1DM, higher dietary omega-3 intake was associated with a reduced risk of islet autoimmunity (HR 0.45; 95% CI 0.21–0.96), while higher omega-3 fatty acid content in erythrocyte membranes was similarly associated with lower risk (HR 0.63; 95% CI 0.41–0.96). However, dietary exposure was assessed from one year of age, and these observational findings do not establish a causal protective effect of neonatal supplementation [59]. The structural integration of EPA and DHA into phospholipid bilayers of immature mucosal cells may influence membrane composition, fluidity, and the availability of substrates for lipid mediator synthesis [2,4].

Omega-3-derived lipid mediators may contribute to the regulation and resolution of inflammatory responses, while ARA-derived mediators also participate in physiological immune signaling and tissue homeostasis. The resulting effects depend on fatty acid balance, cellular context, and developmental stage, rather than a uniform replacement of pro-inflammatory omega-6 fatty acids [57,58]. Although these mechanisms may influence inflammatory signaling and epithelial barrier function, direct evidence that LC-PUFA supplementation suppresses neonatal enteric viral sensing or prevents virus-associated mucosal injury remains insufficient [1,3,57,59]. Furthermore, while limited in vitro studies using human fetal intestinal epithelial cells suggest that LC-PUFAs can attenuate cytokine-induced inflammatory responses, most mechanistic data regarding membrane lipid raft remodeling and tight junction regulation derive from adult cell lines or animal models, and randomized infant supplementation trials have not yet established clinical efficacy for preventing pediatric autoimmune diseases.

Experimental studies in intestinal epithelial and vascular endothelial models indicate that LC-PUFA availability can modulate tight junction organization and barrier-associated proteins—including claudins, occludin, and ZO-1—in a fatty-acid-, dose-, and context-dependent manner [39,60–66]. Hypothetically, optimizing fatty acid balance could help reduce mucosal tissue vulnerability, limit exposure to translocated luminal antigens, and support early peripheral tolerance [59]. However, these mechanistic findings should be distinguished from clinical outcomes in preterm infants. Notably, a systematic review and meta-analysis reported an increased risk of necrotizing enterocolitis with DHA supplementation without concurrent ARA, whereas combined ARA and DHA supplementation was associated with a lower risk in the analyzed studies [67]. Thus, maintaining an appropriate ARA–DHA balance may be particularly relevant to neonatal intestinal health. Nevertheless, whether LC-PUFA-mediated changes in membrane composition and inflammatory signaling reduce enteric viral susceptibility, promote durable immune tolerance, or prevent subsequent T1DM or CD in humans remains unproven.

4.3. Dietary Polyphenols and Mucosal Tissue Homeostasis in Early Life

Beyond macronutrients and essential micronutrients, plant-derived dietary components—including plant-associated RNA viral sequences detected in human feces alongside bioactive phytochemicals such as dietary polyphenols—interact with the intestinal environment during early dietary transitions [68]. In the intestinal mucosa, cytosolic viral nucleic acid sensors such as RIG-I coordinate innate recognition of viral components and downstream inflammatory signaling, while dietary polyphenols introduced via maternal milk or complementary foods are hypothesized to help attenuate secondary oxidative stress [38,69]. Intrinsic antiviral immunity and Type I Interferon signaling pathways require tight homeostatic regulation to prevent chronic mucosal inflammation [70]. Experimental models suggest that dietary polyphenols may help maintain cellular redox balance by scavenging reactive oxygen species, though whether these antioxidant properties translate into clinically meaningful protection against interferon-associated triggers linked to CD and T1DM in human infants remains to be established [71,72].

Beyond general antioxidant activity, specific classes of dietary polyphenols—such as quercetin, resveratrol, and epigallocatechin gallate (EGCG)—have been shown in in vitro and animal studies to interfere with viral replication processes [73]. In cellular models, these bioactive compounds can modulate host intracellular signaling by inhibiting the phosphorylation of mitogen-activated protein kinase (MAPK) pathways, which certain enteric viruses exploit during cellular entry and viral genome translation [74]. By limiting virus-induced signaling perturbations in preclinical systems, polyphenols help preserve epithelial monolayer integrity and reduce tissue sloughing [75].

Additionally, zonulin-mediated disassembly of intercellular tight junctions is a key driver of increased intestinal permeability and paracellular antigen trafficking [76]. Preclinical studies suggest that dietary polyphenols—including anthocyanins—may support mucosal barrier integrity and intestinal mucin (*MUC2*) synthesis, potentially strengthening the physical carbohydrate mucus layer at the juxta-mucosal interface [77,78]. Concurrently, experimental studies indicate that polyphenolic metabolites can interact with innate immune cells, promoting a shift from pro-inflammatory M1 macrophages toward an anti-inflammatory M2 phenotype characterized by increased interleukin-10 (IL-10) secretion [79]. However, because polyphenols exhibit low oral bioavailability, undergo extensive microbial metabolism, and have not been evaluated in controlled neonatal autoimmunity prevention trials, their potential role in early-life mucosal protection should currently be regarded as exploratory.

5. Maternal Dietary Fiber Patterns and SCFAs as Proposed Regulators of the Early-Life Phage Life-Cycle

5.1. Bacteriophage Life-Cycle Dynamics and the Lytic-Temperate Transition in the Newborn Gut

Bacteriophages constitute the vast majority of the human intestinal virome and exert predatory and regulatory control over the surrounding bacterial community immediately after birth [80–82]. During the first 28 days of life, phages navigate the neonatal gut ecosystem using two primary replication strategies: the lytic cycle and the lysogenic cycle [83]. In the dormant lysogenic state, a temperate phage integrates its genetic material into the host bacterial chromosome as a prophage, replicating vertically alongside the host cell without causing immediate structural lysis and co-evolving with its bacterial host [22,83]. Conversely, the lytic cycle results in active viral replication and bacterial cell wall lysis, releasing newly formed virions into the intestinal lumen [83].

In a metabolically stable intestinal tract, lysogeny is thought to predominate across much of the gut phageome, allowing temperate phages to persist while minimizing host immune activation [84]. However, during the neonatal window, this equilibrium remains

dynamic and sensitive to environmental and maternal diet-associated influences [22,85]. In the context of sub-optimal maternal nutrition or maternal systemic inflammation, heightened neonatal luminal oxidative stress has been proposed as a potential destabilizing factor of host–microbiota homeostasis [38,84]. Although oxidative DNA damage and bacterial RecA-mediated cleavage of prophage repressors are recognized triggers of lytic induction in experimental microbiology, their relevance to neonatal host–microbiota immune perturbation remains a working hypothesis [86]. Specifically, the extent to which oxidative stress drives a large-scale temperate-to-lytic phage transition in the human neonatal gut lumen requires direct longitudinal validation [87].

5.2. Potential Pathophysiological Consequences of Lytic Shift: Mucosal Permeability and Neonatal Antigen Leakage

If widespread induction of the phage lytic cycle occurs during the first weeks of life, the resulting wave of bacterial lysis could destabilize the neonatal mucosal barrier [88].

Depending on host specificity and ecological context, phage predation may alter the abundance of early colonizers, though selective depletion of *Bifidobacterium* or *Faecalibacterium* via prophage induction has not yet been confirmed in human neonates [15,27]. In experimental settings, debris from lysed Gram-negative bacteria releases endotoxins—primarily lipopolysaccharides (LPS)—alongside bacterial heat-shock proteins and unmethylated CpG DNA motifs into the juxta-mucosal space [38,81]. In preclinical models, a sudden accumulation of such microbial products can disrupt intestinal epithelial cell function, promoting the disassembly of tight junction protein networks and increasing paracellular permeability [38,39].

Hypothetically, this barrier compromise could create open paracellular channels across the single-cell epithelial sheet, allowing luminal antigens, viral particles, and dietary components to access the lamina propria [39,89]. Once within the sub-epithelial space, translocated microbial and viral motifs can stimulate resident dendritic cells (DCs) through endosomal TLRs, driving their maturation into antigen-presenting cells. In experimental models of autoimmunity, activated DCs migrate to the mesenteric lymph nodes and systemic circulation, where antigen presentation alongside pro-inflammatory cytokines can promote autoreactive responses targeting pancreatic islets or the small intestinal mucosa [11,14,89].

The downstream immunogenic stress associated with extensive bacterial lysis may be further amplified by the release of internal bacterial heat-shock proteins and unmethylated CpG DNA motifs into the lamina propria [28]. While these bacterial components collectively contribute to mucosal inflammation, unmethylated CpG DNA motifs bind with high affinity to endosomal Toll-like Receptor 9 (TLR9), initiating a signaling cascade mediated by the myeloid differentiation primary response 88 (MyD88) adapter protein [90]. In cellular and animal models, this activation drives the nuclear translocation of nuclear factor kappa B (NF-κB), promoting the transcriptional synthesis of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and IL-6 [91].

Sustained local cytokine signaling can in turn destabilize the anchoring protein complexes that maintain epithelial integrity [92]. In experimental inflammatory settings, proteolytic cleavage of claudin networks by matrix metalloproteinases contributes to paracellular tight junction breakdown [93,94]. Under such conditions of increased permeability, macromolecular dietary antigens—such as intact gluten peptides and cow's milk proteins—may bypass normal luminal enzymatic degradation [76]. Upon reaching the sub-epithelial compartment, these antigens are hypothesized to promote a localized pro-inflammatory antigen-presenting milieu that could challenge peripheral self-tolerance checkpoints [95]. Although intestinal barrier dysfunction and altered mucosal immune responses have been investigated in relation to T1DM and CD, a direct mechanistic

pathway linking neonatal prophage induction to subsequent autoimmune disease has not been demonstrated. Importantly, this proposed multi-step cascade—linking luminal oxidative stress and RecA-mediated prophage induction to bacterial lysis, LPS/CpG release, TLR9-driven paracellular permeability, and subsequent autoimmune priming—represents an integrative preclinical hypothesis rather than an established pathway supported by direct human neonatal data.

5.3. Maternal Fiber Intake and SCFA Transmission as Proposed Regulators of Neonatal Phage Dynamics

Because exclusively milk-fed neonates do not ingest solid plant fibers directly, early-life SCFA availability—comprising acetate, propionate, and butyrate—is shaped by two distinct but complementary pathways: vertical maternal transfer and endogenous microbial fermentation within the infant gut [60,96]. During late gestation and lactation, maternal intake of complex dietary fibers—including non-starch polysaccharides, resistant starches, and plant-derived prebiotic fibers shown in maternal–infant cohort and intervention studies to enrich SCFA-producing commensals and elevate circulating and milk SCFA concentrations—fuels anaerobic fermentation in the maternal colon, supporting systemic SCFA availability and potential vertical transfer to the fetus and newborn via the placenta, amniotic fluid, and breast milk [60,96]. Concurrently, pioneering infant gut commensals—most notably *Bifidobacterium* species—ferment HMOs in situ to generate substantial amounts of acetate and lactate, while endogenous butyrate production typically increases more gradually as butyrate-producing taxa expand during late infancy and complementary feeding [23]. Importantly, the relative quantitative contribution of direct maternal SCFA transfer versus in situ neonatal microbial production—and how each source differentially shapes mucosal immune maturation and regulatory T-cell priming—remains incompletely defined [60,96]. Consequently, whereas acetate and lactate predominate in the breastfed neonatal lumen, the epithelial and phage-modulating effects of butyrate are most relevant during late infancy and the transition to complementary solid foods, although maternal transfer may provide low-level early exposure [84,97].

As butyrate availability increases during infant gut maturation, at the epithelial level, butyrate serves as a primary energy source for developing colonocytes, supporting mucosal barrier homeostasis and the stratified inner mucus layer [84,86]. Concurrently, by stimulating mitochondrial oxygen consumption in intestinal epithelial cells, butyrate helps maintain a physiologically hypoxic, reducing microenvironment in the juxta-mucosal lumen [84]. By attenuating local oxidative stress and supporting dense commensal growth—ecological conditions linked to temperate phage persistence in viral ecology models—SCFAs are hypothesized to favor lysogenic stability, although their direct ability to suppress prophage induction in the human neonatal gut remains unproven [87]. Overall, maintaining mucosal redox balance and epithelial integrity is thought to support beneficial commensal populations, limit endotoxin translocation, and protect the immature mucosal immune system from excessive luminal antigen exposure [97,98]. However, whether maternal fiber-derived SCFAs directly prevent phage-mediated bacterial lysis, antigen translocation, or subsequent childhood autoimmunity in humans has not yet been clinically established.

6. Designing Precision Nutritional Protocols

6.1. The Pre-Seroconversion Window and Multi-Omic Risk Stratification

At the intersection of clinical immunology and pediatric research, translating mechanistic hypotheses into prospective cohort designs requires moving beyond single-timepoint cross-sectional profiling toward longitudinal biomarker evaluation [15].

Observational birth cohorts, most notably the prospective TEDDY study, have reported that specific gut virome alterations can be detected prior to the appearance of disease-associated autoantibodies [10,12]. While such temporal precedence suggests an association between early viral exposures and subsequent autoimmune development, observational cohort data alone do not establish causality [10,11]. Investigating this pre-seroconversion window is of particular interest in children carrying high-risk HLA haplotypes, such as HLA-DR3-DR4/DQ8 for T1DM and HLA-DQ2/DQ8 for CD [18,39].

In genetically susceptible populations, persistent or recurrent enteric viral infections—particularly by *Enterovirus* A and B species—have been investigated as candidate environmental co-factors [99,100]. In a systematic review and meta-analysis of observational studies, enterovirus detection was associated with higher odds of clinical T1DM (OR = 6.30; 95% CI: 3.92–10.12) and islet autoimmunity (OR = 3.04; 95% CI: 1.85–5.00), although substantial heterogeneity and potential confounding across study designs warrant cautious interpretation [11,101]. Evaluating this pre-seroconversion period in prospective research cohorts may help clarify whether early nutritional modulation can support mucosal homeostasis before autoantibodies emerge [15,19,20].

Observational birth-cohort analyses suggest that the risk of autoantibody seroconversion is elevated when enteric viral infection coincides with early-life dietary transitions [89]. Mechanistically, it has been hypothesized that concurrent enteric viral replication and dietary antigen introduction (such as gluten) may amplify local mucosal inflammation within the GALT [12]. Under this working model, tissue stress and epitope spreading—potentially involving molecular mimicry between enteroviral capsid motifs and islet autoantigens such as tyrosine phosphatase-like insulinoma antigen (IA-2) and glutamic acid decarboxylase (GAD65)—could contribute to the activation of autoreactive T-cell clones [14,102].

Characterizing this pre-seroconversion period remains a central goal of translational autoimmunity research [19]. Longitudinal stool and serum analyses in birth cohorts indicate that shifts in the gut virome–metabolome axis can be detected up to six months before measurable autoantibodies appear in peripheral blood [10]. Defining this transitional phase provides a conceptual framework for designing future randomized trials to test whether targeted nutritional matrices can support mucosal barrier homeostasis and tight junction integrity prior to irreversible pancreatic beta-cell or small intestinal tissue injury [76].

6.2. Conceptualizing a Multi-Omic Laboratory Biomarker Framework for Research Surveillance

Translating these mechanistic insights into a multi-omic biomarker strategy would depend on the longitudinal timing and analytical precision of laboratory assays, potentially starting within the neonatal period (the first 28 days of life) and extending through early infancy within structured prospective research cohorts [10,15]. Rather than relying on isolated cross-sectional measurements, a proposed research protocol could establish baseline sampling using pioneer neonatal meconium and week-4 stool specimens to characterize initial prophage induction dynamics and maternal antibody transfers [22,27,31]. Subsequent longitudinal sampling at months 3, 6, 12, and 24 could systematically map transitions from an exclusive milk diet to complementary solid food matrices [11,28,29].

Within such an investigative framework, longitudinal deep viromic profiling would track shifts in the ratio between prokaryotic bacteriophages and expanding eukaryotic viruses, where a pronounced inversion of this ecological balance could be evaluated as a candidate early indicator of mucosal vulnerability [28,103]. Concurrently, gas chromatography–mass spectrometry (GC-MS) could quantify fecal and urinary short-chain fatty acid profiles to explore whether sustained declines in absolute butyrate concentrations correlate with thinning of the protective inner mucus layer [86,96]. Finally, localized tissue

stress could be assessed in research settings using digital droplet PCR (ddPCR) of peripheral blood mononuclear cells to monitor a candidate panel of interferon-stimulated genes, including IFI44L, ISG15, and OAS1 [16,17]. Whether statistically significant up-regulation of these transcripts reliably defines a sub-clinical interferonopathy capable of stratifying risk prior to autoantibody seroconversion remains to be validated in prospective clinical studies [15,17]. Importantly, these candidate viromic signatures, SCFA profiles, and interferon-stimulated gene panels must currently be regarded as exploratory research biomarkers rather than validated clinical predictors. Before such a multi-omic framework can be translated into pediatric autoimmune risk stratification, several methodological and clinical prerequisites must be met: (i) rigorous standardization of pre-analytical sample collection, nucleic acid extraction, and bioinformatic or metabolomic quantification pipelines across laboratories; (ii) establishment of age-specific reference ranges and clinically meaningful diagnostic thresholds that distinguish transient physiological fluctuations from true pre-autoimmune pathology; and (iii) independent replication and cost-effectiveness evaluation across large, ethnically and geographically diverse longitudinal birth cohorts (Table 1).

Table 1. Proposed Longitudinal Multi-Omic Research Surveillance Framework for Genetically Predisposed Neonates.

Biomarker Layer	Specific Target Analyte	Laboratory Methodology	Proposed Sampling Interval	Candidate Biomarker Shift for Research Stratification
Viromic Deep Sequencing	Eukaryotic *Enterovirus A* and *B* viral titers; Caudoviricetes/Microviridae ratio	HTS	Baseline neonatal meconium (Days 1–3), followed by week 4, month 3, and month 6 profiles	Exploratory relative shift in the phage-to-eukaryotic virus ratio alongside rising enteroviral expansion patterns (diagnostic cut-off unestablished) [10,22,28,103]
Targeted Metabolomics	Fecal and urinary short-chain fatty acids (absolute butyrate, acetate, propionate levels)	GC-MS	Month 3, month 6, and month 12 milestones	Candidate downward trajectory in fecal butyrate concentrations relative to age-matched longitudinal cohort distributions (reference range unvalidated) [60,96].
Peripheral Blood Transcriptomics	Interferon-stimulated gene signature (IFI44L, ISG15, and OAS1 mRNA expression)	ddPCR	Screening performed at neonatal week 4, month 3, and month 6 checkpoints	Exploratory relative up-regulation of target transcripts suggestive of a sub-clinical interferon signature (diagnostic threshold unestablished) [15–17]

HTS: High-throughput shotgun virome sequencing; GC-MS: Gas chromatography-mass spectrometry; ddPCR: Digital droplet polymerase chain reaction.

6.3. Investigational Precision Nutritional Regimens for High-Risk Interception

When multi-omic research monitoring identifies an infant with candidate risk signatures—such as elevated enteroviral loads, altered SCFA profiles, and an emerging inflammatory transcriptomic pattern—tailored nutritional regimens represent an investigational preventive strategy that warrants evaluation in controlled clinical trials rather than current clinical practice.

6.3.1. Bioactive HMO Core

Within experimental trial designs, the infant's diet could be supplemented with structurally defined HMOs, specifically 2′-FL and LNnT. In human milk, 2′-FL concentrations typically range around 2.0–2.5 g/L in secretor-positive mothers, whereas LNnT is generally present at substantially lower concentrations, often below 0.5 g/L [104,105].

For infant formula supplementation, clinically evaluated concentrations of 1.0 g/L 2′-FL and 0.5 g/L LNnT (2:1 ratio) have demonstrated adequate growth and tolerability in randomized clinical trials [106,107].

These concentrations are selected based on safety and tolerability data rather than to replicate the full physiological HMO diversity of human milk; notably, a recent critical evaluation of randomized clinical trials concluded that evidence for clinical benefits of human-identical milk oligosaccharide supplementation in infants remains limited, and efficacy in preventing autoimmunity is unproven [22,108–110]. Preclinically, specific fucosylated and sialylated HMOs have been experimentally shown to act as soluble receptor decoys against selected norovirus and rotavirus genotypes, whereas direct experimental evidence for competitive decoy binding against enteroviruses remains limited and largely hypothetical [12,22,23,40]. Structurally diverse HMOs, such as sialylated variants like 3′-SL and 6′-sialyllactose (6′-SL), may act alongside neutral fucosylated glycans to support mucosal defense [23]. While sialylated HMOs have been shown in vitro to bind certain sialic-acid-dependent virions—such as specific rotavirus strains and enterovirus 71 in cellular assays—whether fucosylated or sialylated HMOs directly inhibit attachment or entry of diabetogenic enteroviruses in vivo remains to be established [111]. Furthermore, experimental studies indicate that certain HMOs can modulate epithelial gene expression, up-regulating focal adhesion kinase (FAK) pathways associated with epithelial cell migration and repair [112,113].

6.3.2. VDR Ligands

Because genetic susceptibility to early-life autoimmunity may be amplified by dysregulated viral sensing and persistent mucosal stress, optimizing vitamin D status has been proposed as a supportive component of investigational prevention protocols [6]. Currently, oral cholecalciferol (Vitamin D3) is recommended at 400 IU/day for healthy term infants to prevent vitamin D deficiency, with higher doses (up to 1000 IU/day) considered only when clinically indicated under medical supervision. Although serum 25(OH)D concentrations of 40–60 ng/mL have been discussed in relation to potential immunomodulatory benefits [6,45], this range has not been validated as a therapeutic target in neonates, and its role in preventing pediatric autoimmunity remains unproven. At the molecular level, active vitamin D3 (calcitriol) binds to the intracellular vitamin D receptor (VDR), modulating gene transcription and immune signaling pathways involved in mucosal homeostasis [47]. In experimental settings, calcitriol–VDR signaling modulates innate immune pathways and pattern recognition receptor expression (including endosomal TLRs) in a cell- and stimulus-dependent manner rather than uniformly suppressing antiviral responses [17,46,47,55,114,115]. While selected preclinical models suggest that VDR activation can dampen secondary inflammatory cascades under specific conditions, direct evidence that vitamin D supplementation attenuates viral nucleic acid sensing, suppresses persistent Type I Interferon signatures, or prevents autoimmune seroconversion in human infants remains insufficient [47,116].

6.3.3. Membrane-Stabilizing Omega-3 PUFAs

The potential immunomodulatory role of LC-PUFAs, particularly EPA and DHA, also remains under investigation in early life, and no specific combined dose (such as 40–50 mg/kg/day) has been validated for neonatal antiviral defense or autoimmunity prevention. Mechanistically, these fatty acids may influence intestinal epithelial membrane organization and immune signaling [1,4,57]. By incorporating into cellular lipid bilayers and modifying membrane fatty acid composition while preserving the essential developmental functions of ARA, LC-PUFAs can alter membrane fluidity and affect cholesterol-rich lipid rafts in experimental systems [1,4,57,59]. Because these specialized microdomains

serve as platforms for viral assembly and endocytic entry in cellular models, their structural modulation could theoretically influence viral receptor clustering [117,118]. However, whether EPA and DHA incorporation alters viral entry or cellular stress signaling in human neonatal enterocytes remains to be established [119]. Concurrently, omega-3-derived metabolites can act as ligands for peroxisome proliferator-activated receptor gamma (PPAR-γ) in preclinical models, attenuating pro-inflammatory transcription and supporting paracellular tight junction integrity (Table 2) [120,121]. Nonetheless, these effects are supported primarily by experimental data and have not been established as clinical outcomes of neonatal supplementation. Furthermore, the candidate biomarker layers outlined in Table 1 and the investigational nutritional components summarized in Table 2 should be viewed as a hypothesis-generating research pairing rather than an actionable clinical decision algorithm. At present, no validated diagnostic thresholds, age-adjusted reference intervals, or formal sample-size calculations exist to link a specific biomarker perturbation in Table 1 to a standardized nutritional prescription in Table 2. Defining actionable decision rules will require multi-stage prospective validation—beginning with observational discovery cohorts powered to establish receiver-operating characteristic (ROC) cutoffs and longitudinal predictive values, followed by biomarker-stratified randomized controlled trials. In addition, operationalizing this framework presupposes early genetic risk identification; however, universal neonatal HLA screening remains largely restricted to research registries due to cost, limited positive predictive value (as most HLA-risk carriers never develop disease), informed-consent complexities, and potential parental psychosocial burden. Finally, although T1DM and CD share overlapping mucosal barrier vulnerabilities, future validation studies must stratify these conditions separately given their distinct primary environmental triggers—specifically enteroviral tropism in T1DM versus dietary gluten introduction alongside viral co-factors in CD.

Table 2. Summary of Investigational Precision Immunonutritional Components, Targets, and Proposed Biological Effects Across Neonatal and Early Infancy Windows.

Dietary/Nutritional Component	Targeted Mucosal Element	Proposed Mechanistic Action on Gut Virome & Mucosa	Potential Biological Effects and Research Implications	Primary Target Window & Population
HMOs (2′-FL & LNnT)	Enterocyte Brush Border Glycocalyx & HBGA Receptors	Soluble decoy activity demonstrated experimentally for specific norovirus and rotavirus genotypes; direct inhibition of T1DM/CD-associated enteroviruses remains unproven [12,15,22,23,40]	Hypothesized to limit epithelial attachment, support tight junction integrity, and reduce paracellular antigen leakage (preclinical data, including reduced autoimmune diabetes incidence in NOD mice; human efficacy unproven)	Neonatal phase to early infancy (Days 1–28 and onwards) in research cohorts
Cholecalciferol (Vitamin D3)	Intestinal VDR & Mucosal Immune Cells	Modulates innate immune signaling and receptor expression in a cell- and stimulus-dependent manner (experimental data; direct viral-sensing suppression unestablished) [6,17,45–47,55]	Supports mucosal immune homeostasis and Treg regulation; attenuation of interferon signatures or autoimmunity risk in infants remains unproven	Initiated in the neonatal window (400 IU/day standard prophylaxis) in high-risk HLA cohorts
LC-PUFAs (Balanced DHA & ARA)	Host Immune Cell Plasma and Endosomal Lipid Bilayers	Modulates membrane phospholipid composition and lipid raft organization while preserving physiological ARA–DHA balance	Hypothesized to attenuate pro-inflammatory signaling and support tight junction integrity (infant autoimmunity prevention unproven)	Infancy window following early neonatal multi-omic stratification

		(experimental data) [1,4,57,59,117–121]		
Complex Dietary Fibers (Prebiotics)	Juxta-mucosal Mucus Layer (MUC2) & Anaerobic Matrix	Promotes SCFA synthesis, reducing oxidative stress and hypothesized to favor temperate lysogeny [60,84,86,87,96]	Supports protective pioneer commensal bacteria and helps limit endotoxin (LPS) translocation	Maternal diet modulation during gestation/lactation, and infant solid food transition

HMOs: Human Milk Oligosaccharides; HBGA: Histo-Blood Group Antigen; VDR: Vitamin D Receptor; SCFA: Short-Chain Fatty Acid; PUFAs: Polyunsaturated Fatty Acids; 2′-FL: 2′-fucosyllactose; LNnT: Lacto-*N*-neotetraose; ARA: Arachidonic Acid; DHA: Docosahexaenoic Acid; LC-PUFAs: Long-Chain Polyunsaturated Fatty Acids.

7. Future Perspectives

Translating these mechanistic hypotheses into neonatal clinical care will require moving beyond descriptive pediatric cohort profiling toward rigorously designed, prospective multi-omic clinical trials initiated in early life [10,11]. A key research priority in translational neonatology is evaluating whether standardized, non-invasive biomarker pipelines can reliably stratify risk during the neonatal period. Experimental workflows integrating longitudinal viromic sequencing of pioneer newborn meconium, gas chromatography–mass spectrometry (GC-MS) of neonatal SCFA profiles, and peripheral blood expression profiling of interferon-stimulated transcripts offer a promising research approach to map early viral–metabolic trajectories [15,16,96]. In future prospective studies, such multi-omic profiling could help determine whether asymptomatic enteroviral colonization or reduced maternal-derived butyrate availability precedes sub-clinical mucosal stress by several months [89,99].

Furthermore, future maternal–neonatal nutrition research should evaluate the interactive effects of combinatorial milk matrices rather than isolated micronutrients alone. Controlled clinical trials are needed to investigate whether maternal lipid enrichment, defined HMO blends, and fermentable prenatal dietary fibers act synergistically to support immature enterocyte barrier function [23]. Advanced metabolomic studies will also be necessary to establish safe, evidence-based maternal and infant dosing strategies—as optimal dosages and long-term clinical efficacy remain unestablished—and to test whether dietary modulation can maintain prokaryotic bacteriophages in a benign, temperate lysogenic state in infants carrying high-risk HLA susceptibility alleles [84,87]. In addition, experimental virome-targeted interventions—such as maternal fecal virome transplantation (FVT) in Cesarean-born newborns—must be approached with particular caution and remain strictly preclinical or experimental [31,33]. Specifically, administering complex viral filtrates to neonates with an immature mucosal barrier and developing immune system raises substantial developmental safety concerns, including the potential inadvertent transfer of uncharacterized eukaryotic viruses, temperate phages carrying antimicrobial resistance or virulence genes, and unexpected perturbations of bacterial–phage co-evolution. Moreover, FVT faces major ethical and regulatory hurdles—including the lack of standardized donor-screening protocols, batch-to-batch compositional reproducibility, formal regulatory classification, and rigorous risk–benefit justification in vulnerable newborn populations—that must be resolved before clinical translation can be contemplated [31,33]. Exploring how to foster a resilient neonatal gut ecosystem during the first weeks of life represents a promising avenue for primary prevention research, though its safety and efficacy in reducing early-onset pediatric autoimmunity remain to be proven [1,60,97].

Finally, operationalizing complex multi-omic datasets in future research cohorts may benefit from artificial intelligence-driven analytical tools [122]. Integrating maternal dietary records, newborn viromic profiles, and genetic risk markers into validated machine-learning models could eventually help researchers generate individualized mucosal risk scores [10]. However, such digital tools will require extensive external validation, standardization, and ethical oversight before they can be translated into routine neonatal care or used to guide precision nutritional interventions aimed at lowering the burden of pediatric autoimmunity [123].

8. Conclusions

Early life—spanning the neonatal period through infancy and early childhood (the first two to three years of life)—represents a sensitive developmental continuum during which maternal dietary patterns, infant feeding trajectories, and complementary food transitions act as key environmental modulators of the gut virome ecosystem. Accumulating observational and experimental evidence suggests that disruptions in early viral–bacterial homeostasis—characterized by opportunistic eukaryotic viral expansion and potential shifts toward bacteriophage lytic activity—may act as environmental co-factors in early-life autoimmunity. In genetically predisposed infants and young children carrying high-risk HLA genotypes, persistent mucosal stress is hypothesized to promote a chronic pro-inflammatory state that degrades tight junction networks, increases paracellular antigen leakage across the developing intestinal barrier, and impairs peripheral self-tolerance, potentially accelerating the clinical onset of pediatric conditions such as T1DM and CD. Precision nutritional immunology provides a promising, non-invasive conceptual framework to investigate how early dietary modulation might mitigate these environmental triggers across infancy and early childhood. Rather than relying solely on passive observation, targeted nutritional strategies aim to support mucosal resilience across multiple biochemical levels. Preclinical data suggest that luminal shielding via structured HMOs can intercept selected enteric viruses (primarily norovirus and rotavirus strains) in the gut fluid, helping to limit epithelial docking and preserve physical barrier integrity. Concurrently, experimental studies suggest that vitamin D3 modulates mucosal immune signaling in a context-dependent manner, while dietary long-chain PUFAs integrate into cell membranes to help regulate inflammatory pathways—though direct clinical evidence that these nutrients suppress enteric viral sensing or attenuate persistent Type I Interferon signatures in human infants remains insufficient. At the metabolic level, maternal and early-life dietary fiber patterns support SCFA availability, which is hypothesized to help maintain mucosal anaerobiosis and favor temperate phage dynamics. Validating these age-tailored precision dietary regimens through prospective longitudinal trials in well-defined term and preterm cohorts will be essential to determine whether early-life virome and metabolome screening can be translated into an effective preventive protocol to reduce the global burden of early childhood autoimmune diseases.

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