

REVIEW ARTICLE

Developmental symbiosis in immunity:
Microbiome–immune interactions from infancy
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Abstract

The maturation of the immune system is not an isolated, genetically pre-programmed process but rather the outcome of a deeply integrated partnership between host and microbial communities, a phenomenon we term developmental symbiosis. This review synthesizes evidence from evolutionary biology, ecology, and immunology to describe how symbiotic relationships shape immune trajectories across the human lifespan. We begin by addressing the co-evolutionary foundations of this partnership, illustrating how ancient microbial encounters drove the selection of key molecular components, including pathogen-associated molecular pattern recognition by Toll-like receptors (TLRs) and the viral origins of recombination-activating genes. Moving away from a siloed structure, we examine the lifespan chronologically, integrating mechanistic insights with clinical pathology for each developmental window. We detail the unique immune behaviors of the prenatal period, specifically the window of heightened tolerance, followed by the critical priming events of neonatal colonization, the expansive education of infancy, the hormonal modulations of adolescence, and the dysbiotic shifts of aging. Within each stage, we highlight how environmental disruptions, such as antibiotic use or delivery mode changes, can permanently recalibrate immune set-points. Finally, we evaluate the current status of therapeutic modulations, including probiotics and fecal microbiota transplantation, emphasizing the need for precision interventions that are tailored in accordance to the temporal specificity of immune development.

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1. Introduction

The immune system's principal role has traditionally been framed as defense: a sophisticated surveillance network designed to detect and neutralize harmful invaders. However, this “battlefield” perspective tells only part of the story. Equally fundamental to immune function is the ability to live in harmony with an extensive and diverse community of microorganisms (bacteria, archaea, fungi, protozoa, and viruses) that

inhabit every mucosal and epithelial surface of the body. This coexistence is not incidental; it is the product of a deep evolutionary partnership in which immune maturation depends on a steady influx of microbial cues, and microbial persistence depends on immune tolerance and spatial compartmentalization.^{1,2}

The concept of developmental symbiosis frames immune ontogeny as a co-constructed process: host genetic programming sets the developmental blueprint, but microbial partners provide essential signals that refine, calibrate, and sometimes even initiate immune functions. Evidence from germ-free animal models, dating back to landmark mid-20th century experiments by Reyniers and Gordon at the LOBUND Institute, demonstrates that the absence of microbiota leads to profound defects in lymphoid organ development, immune cell differentiation, and mucosal defense.³⁻⁵ Subsequent research has revealed that microbial influence begins earlier than previously thought, potentially during gestation, and continues to modulate immunity across the lifespan.

In parallel, epidemiological patterns have hinted at the consequences of disrupted developmental symbiosis. The rapid rise in immune-mediated conditions, such as allergies, asthma, inflammatory bowel disease (IBD), and certain autoimmune disorders, in industrialized societies has been linked to reduced microbial diversity and altered colonization patterns in early life.^{6,7} These shifts are thought to stem from modern practices including increased Cesarean section rates, widespread antibiotic use, urbanized living, and dietary changes.⁸

Despite the growing body of evidence, much of the literature remains siloed. Microbiome research often focuses on composition and diversity metrics, while immunology tends to prioritize cellular and molecular pathways. Developmental symbiosis as a unifying concept integrates these perspectives, emphasizing the bidirectional and temporal nature of host-microbe interactions. To facilitate this cross-disciplinary dialogue, we first define

key immunological players that will appear throughout this review (Table 1).

2. Evolutionary and ecological basis

2.1. Co-evolutionary foundations

The immune system is the product of evolutionary pressures exerted not only by pathogens but by a complex community of commensal and mutualistic microorganisms. Over millions of years, vertebrates and their microbial partners have developed reciprocal signaling systems that maintain homeostasis while preserving the capacity to mount rapid defensive responses.⁹

Classical examples from molecular immunology illustrate this co-evolutionary imprint. Toll-like receptors (TLRs) show clear patterns of positive selection at residues directly involved in pathogen-associated molecular pattern (PAMP) recognition. Comparative genomics reveals that different vertebrate lineages have independently diversified TLR repertoires in response to the particular microbial environments they encountered; for instance, TLR4 and TLR5 are classic examples of receptors that have evolved rapidly in regions responsible for binding bacterial lipopolysaccharide (LPS) and flagellin, respectively.⁸ A similar co-evolutionary imprint is seen in the germline repertoire of immunoglobulin heavy-chain variable region (VH) genes. Certain VH families retain conserved motifs that bias antibody responses toward common pathogen epitopes, suggesting that recurrent encounters with specific classes of microbes shaped the ancestral germline configuration. A final classical example is that of the recombination-activating genes (RAG), essential for V(D)J recombination, which appear to derive from the domestication of a transposon related to ancient DNA viruses, marking a definitive moment where a foreign genetic element was co-opted to drive adaptive immune diversity.^{9,10}

In humans, the gut-associated lymphoid tissue appears to have evolved under the influence of these dense

Table 1. A primer on immune players

Concept	Definition
Inflammation	A protective response to injury or infection. Chronic low-grade inflammation is a maladaptive state linked to aging and metabolic disease.
Innate vs. adaptive immunity	The innate system (e.g., macrophages, neutrophils) provides immediate, non-specific defense, while the adaptive system (T and B cells) offers specific, memory-based protection.
Regulatory T cells (Tregs)	A specialized subpopulation of T cells that act as “brakes” on the immune system, preventing autoimmune reactions and maintaining tolerance to commensal microbes.
Th1, Th2, and Th17	Subsets of helper T cells that direct different immune responses. Th1 targets intracellular pathogens; Th2 targets parasites (and drives allergies); Th17 fights extracellular bacteria/fungi but is implicated in autoimmunity.

microbial communities, with structural features, such as Peyer's patches, optimized for sampling luminal antigens.¹¹ This relationship forms the basis of the "Old Friends" hypothesis, formulated by Graham Rook and colleagues, which posits that many aspects of immune regulation, including the development of regulatory T cells (Tregs), were shaped by long-standing exposure to non-pathogenic microbes encountered throughout human evolutionary history.¹² The disappearance of these microbial partners in modern environments may unmask latent vulnerabilities in immune tolerance mechanisms, predisposing individuals to chronic inflammation and autoimmunity.

2.2. Cross-kingdom signals

Microbial influence on immunity is mediated through an intricate network of cross-kingdom signals. Bacterial quorum-sensing molecules, such as N-acyl homoserine lactones, can modulate cytokine production in host epithelial cells.¹³ Fungal cell wall components, notably β -glucans, are potent activators of dectin-1-dependent pathways that contribute to trained innate immunity.¹⁴ Even viruses, often overlooked in the context of mutualism, can exert immunomodulatory effects; for example, non-pathogenic bacteriophages may indirectly shape immune tone by altering bacterial community composition.¹⁵ These signals are not mere "noise"; they are integral developmental inputs that help establish set-points for inflammatory thresholds, antimicrobial peptide expression, and mucosal barrier integrity.

2.3. Developmental symbiosis in the animal kingdom

Non-human models provide compelling demonstrations that developmental symbiosis is a conserved biological strategy. The Hawaiian bobtail squid *Euprymna scolopes* selectively recruits the luminescent bacterium *Vibrio fischeri*, which in turn shapes the squid's light organ morphology through microbe-derived signals. In deep-sea tubeworms (*Riftia pachyptila*), the absence of a digestive system necessitates a complete reliance on intracellular bacterial symbionts, maintained by highly specialized immune tolerance pathways.¹⁶ Similarly, germ-free zebrafish fail to develop normal gut vascularization until colonized with commensal microbes, underscoring the cross-organ developmental influence of microbiota.¹⁷ These examples highlight that the mechanisms underlying human immune-microbe development are deeply rooted in evolutionary history.

3. The arc of developmental symbiosis

A central feature of developmental symbiosis is its temporal specificity. The immune system passes through discrete stages of maturation in which it is uniquely receptive to microbial signals. We here examine the lifespan chronologically, integrating the specific mechanisms and potential disruptions relevant to each developmental window (Table 2). The developmental timeline of microbiota-immune crosstalk is illustrated in Figure 1.

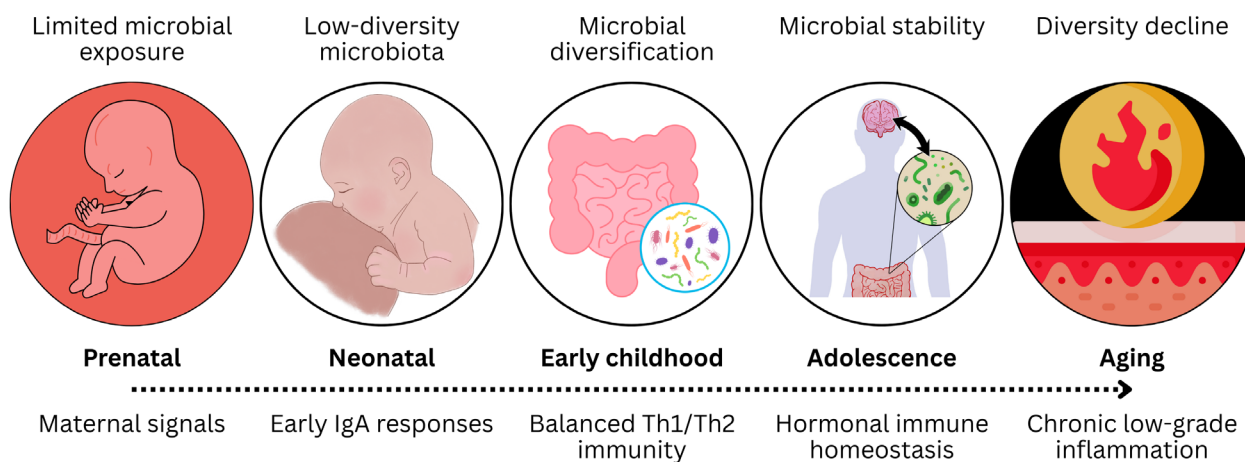


Figure 1. Developmental timeline of microbiota-immune crosstalk. This schematic illustrates the relationship between the gut microbiota and host immune system across five life stages. During the prenatal period, maternal signals and limited microbial exposure shape fetal immune tolerance. In the neonatal stage, low-diversity microbiota dominated by *Bifidobacterium* prime regulatory T cells and early IgA responses. Early childhood is marked by rapid microbial diversification, balanced Th1/Th2 immunity, and expansion of adaptive memory. In adolescence, microbial composition approaches adult-like stability, while pubertal hormones modulate immune homeostasis. In aging, microbiota diversity declines, short-chain fatty acid (SCFA) producers are reduced, and immune senescence with chronic low-grade inflammation ("inflammaging") emerges. Together, these transitions highlight the reciprocal influences of microbes and immunity across human development. Image created by authors using Adobe Illustrator.

3.1. Prenatal stage: Metabolic priming and tolerance

For much of the 20th century, the intrauterine environment was considered sterile. While the existence of a true *in utero* microbiome remains debated, current consensus suggests that microbial products, such as short-chain fatty acids (SCFAs) and LPS, can reach the fetus via maternal circulation.^{18,19} This prenatal stage represents an indirect symbiotic influence, where maternal–microbial interactions shape the immune landscape into which the infant will be born.²⁰

It is critical to note that the immune system responds differently depending on age. During early organismal development, the immune system passes through a distinct window of heightened tolerance. In mammals, this period spans fetal life and the early neonatal phase, when the adaptive immune system is still maturing and regulatory pathways dominate over effector responses. Antigens encountered during this window, especially those that are persistent or presented in a non-inflammatory context, tend to be imprinted as “self” or harmless, shaping long-term immunological tolerance.

Mechanistically, this priming is often mediated by metabolites. Maternal gut-derived acetate can cross the placenta and influence fetal immune programming, particularly promoting the development of fetal Tregs through epigenetic modulation of the *FOXP3* gene. Germ-free mouse models demonstrate that depletion of maternal microbiota alters offspring mucosal immunity, including reduced numbers of type 3 innate lymphoid cells (ILC3s) and impaired epithelial barrier maturation.²¹ Furthermore, maternal exposure to environmental microbes (via diet, contact with animals, or rural living) has been correlated with reduced allergy risk in offspring, potentially mediated by altered maternal cytokine profiles that pass through the placenta. Conversely, disruption at this stage, through maternal antibiotics, poor diet, or dysbiosis, could alter the baseline immune calibration before the first direct colonization even occurs.²²

3.2. Birth and neonatal: The first colonization

Birth represents the most abrupt ecological transition in human life, marking the first sustained contact between the newborn and a complex external microbial world. This initial colonization event, described over a century ago by Henry Tissier, who first isolated *Bifidobacterium* from the stools of breastfed infants, sets the trajectory for early immune education.²³

3.2.1. The perinatal transition

The mode of delivery exerts a profound influence on the initial microbial community. Vaginally delivered infants

acquire a microbiota dominated by maternal vaginal and intestinal taxa (e.g., *Lactobacillus*, *Bacteroides*), whereas those delivered by Cesarean section (C-section) are initially colonized by skin- and hospital-associated species like *Staphylococcus* and *Corynebacterium*.²⁴

These distinct microbial communities influence immune priming within hours. Neonates delivered vaginally display higher expression of Toll-like receptor (TLR)–related genes and greater interleukin (IL)-10 production in cord blood mononuclear cells compared with their C-section counterparts. Furthermore, natural killer cell receptor repertoires appear more diverse in vaginally delivered infants, suggesting an immediate influence of microbial contact on innate immune education.^{25,26}

3.2.2. Mechanisms of education: Breast milk and *Bifidobacteria*

Following birth, feeding method becomes the primary driver of symbiosis. Breast milk acts not only as a nutrient source but as an immunological blueprint, delivering secretory IgA (sIgA), lactoferrin, cytokines, and a complex suite of human milk oligosaccharides (HMOs).²⁴ HMOs selectively nourish beneficial gut bacteria, particularly *Bifidobacterium longum* subsp. *infantis*. This strain promotes the expansion of IL-10-secreting Tregs, potentially mitigating excessive inflammatory responses during this sensitive window.^{27–29}

3.2.3. Disruptions: C-sections and antibiotics

Deviations from this evolutionary script can leave lasting immunological imprints. C-section delivery has been linked to delayed colonization by obligate anaerobes and suboptimal IgA coating patterns in the gut lumen. Epidemiologically, this correlates with increased risks of asthma, allergic rhinitis, and type 1 diabetes.³⁰ Similarly, perinatal antibiotic exposure, whether maternal intrapartum prophylaxis or neonatal therapy, induces abrupt shifts, often characterized by a loss of *Bifidobacterium* and an overgrowth of facultative anaerobes like *Enterococcus*. Murine models demonstrate that such transient depletion can lead to long-term defects in IgA production and heightened systemic inflammatory responses.³¹

3.3. Infancy and weaning: Education and expansion dietary diversification and oral tolerance

The introduction of solid foods (weaning) represents a profound ecological inflection point. As dietary complexity increases, the microbiome shifts toward taxa specialized in complex carbohydrate fermentation, such as *Ruminococcus* and *Faecalibacterium*. This diversification is critical for the establishment of oral tolerance, the immune

system's ability to remain unreactive to food antigens while maintaining vigilance against pathogens.^{32,33}

Mechanistically, the expansion of butyrate-producing *Clostridiales* during this phase reinforces epithelial barrier function and promotes the induction of antigen-specific Tregs via dendritic cell sampling in the mesenteric lymph nodes.³⁴ This period reflects the "Hygiene Hypothesis" (originally proposed by David Strachan in 1989) which suggests that limited exposure to microbial stimuli during early childhood hinders the natural shift from a Th2-biased (allergic) immune profile toward a balanced Th1/regulatory profile.³⁵

3.3.1. Vulnerabilities: Diet and infection

Disruptions during weaning can derail this educational process. The introduction of ultra-processed foods, high in refined sugars and low in fiber, reduces microbial diversity and SCFA availability, impairing barrier function. Such "westernized" dietary patterns in early childhood are associated with pediatric obesity and metabolic syndrome features.^{36,37} Additionally, antibiotic exposure during this window is associated with increased risks of inflammatory bowel disease (IBD) and asthma in longitudinal cohorts. Conversely, viral infections like respiratory syncytial virus (RSV) can skew immune memory toward Th2 responses, while rotavirus vaccination has been surprisingly linked to a reduced risk of type 1 diabetes, possibly via preservation of gut epithelial integrity.^{38,39}

3.4. Adolescence: Hormonal modulation puberty and the "estrobolome"

Adolescence is an often-underappreciated immunological milestone. While the core immune architecture is established in childhood, the pubertal surge in sex steroids reshapes mucosal immunity. Sex hormones influence the composition of the microbiota; estrogens, for instance, increase the abundance of *Bacteroides* and *Lactobacillus* species.^{40,41} These bacteria, in turn, possess β -glucuronidase enzymes capable of deconjugating estrogens, modulating their enterohepatic circulation, a feedback loop termed the "estrobolome."

3.4.1. Specific vulnerabilities: Stress and lifestyle

This stage is characterized by lifestyle-dependent plasticity. Adolescence often brings increased exposure to psychosocial stress, which dysregulates the hypothalamic-pituitary-adrenal (HPA) axis. Elevated cortisol levels can increase intestinal permeability ("leaky gut") and shift the Th17/Treg balance toward inflammation.⁴² Furthermore,

behaviors such as alcohol consumption and substance use can directly disrupt gut tight junctions and reduce beneficial *Faecalibacterium prausnitzii*. These disruptions occur just as autoimmune risks (e.g., multiple sclerosis, lupus) often accelerate, potentially linked to these hormonally mediated shifts in immune tolerance.⁴³

3.5. Aging: Immunosenescence

As the lifespan extends, the symbiotic partnership inevitably deteriorates. Aging is characterized by immunosenescence (declining immune function) and inflammaging (chronic low-grade inflammation).⁴⁴ These phenomena parallel microbial shifts: reduced diversity, increased pathobiont abundance, and decreased SCFA production. The breakdown of the immune-microbe détente reduces colonization resistance and promotes barrier dysfunction, creating a feedback loop that accelerates frailty and cognitive decline. Whether these changes are drivers or consequences of aging remains active research, but dietary interventions suggest at least partial reversibility.⁴⁵

4. Therapeutic modulation of the microbiota-immune axis

The growing understanding of the microbiota-immune interface has shifted therapeutic strategies in immunology and neurology from symptom management to ecosystem modulation.⁴⁶ Rather than targeting a single pathogen or pathway, interventions now aim to recalibrate the microbial community and its molecular crosstalk with the host. However, it is vital to distinguish between established clinical protocols and approaches that remain experimental.^{47,48}

4.1. Probiotics, prebiotics, and synbiotics

Probiotics have shown promise in modulating systemic and neuroimmune responses, though clinical translation lags behind preclinical success. In animal models, specific strains such as *Lactobacillus rhamnosus* GG and *Bifidobacterium breve* A1 effectively enhance anti-inflammatory cytokine production and increase Treg activity. In humans, the evidence is more variable.⁴⁹ For example, while meta-analyses support the use of probiotics for preventing antibiotic-associated diarrhea, their efficacy in modulating complex immune-mediated diseases is still under investigation. Early-phase clinical trials in multiple sclerosis have demonstrated that probiotic supplementation can reduce peripheral pro-inflammatory cytokines (TNF- α , IL-6) and improve quality-of-life scores, but these preliminary findings require phase III validation.⁵⁰

Table 2. Developmental windows of microbiota–immune interactions

Developmental stage	Microbial features	Immune milestones	Clinical implications	Key references
Prenatal	Low-diversity, debated presence of <i>in utero</i> microbiota; strong maternal influence via placenta, amniotic fluid, and metabolites	Fetal tolerance development; priming of innate immunity	Maternal diet, antibiotics, and metabolic status may program offspring immune risk	20–23
Neonatal (0–1 year)	Rapid colonization by <i>Bifidobacterium</i> and <i>Lactobacillus</i> ; breast milk oligosaccharides enrich specific taxa	Treg expansion; Th1/Th2 balance calibration; IgA production	Cesarean delivery, formula feeding, and antibiotics linked to allergies and autoimmunity	24–30
Early childhood (1–5 years)	Diversification of gut microbiota; increasing microbial complexity resembling adults	Maturation of adaptive immunity; expansion of memory T and B cells	Dysbiosis at this stage may predispose to asthma, IBD, and eczema	36–39
Adolescence (10–19 years)	Hormonal changes reshape gut and skin microbiota; sex differences emerge	Refinement of immune repertoire; immune surveillance adaptations	Links to acne, autoimmunity, metabolic inflammation	40–43
Adulthood (20–65 years)	Stable, individualized microbiota	Immune homeostasis; balance of tolerance and defense	Dysbiosis linked to chronic inflammatory disease, cancer, and metabolic syndromes	45–50
Aging (≥65 years)	Reduced microbial diversity; decline in SCFA producers	Immunosenescence; chronic low-grade inflammation (“inflammaging”)	Associated with frailty, reduced vaccine responses, and neuroinflammation	51–54

Abbreviations: IBD: Inflammatory bowel disease; SCFA: Short-chain fatty acid; Treg: Regulatory T cell.

Prebiotics (non-digestible food components like inulin) selectively stimulate beneficial commensals, increasing SCFA production and enhancing epithelial barrier integrity.⁵⁸ Synbiotics, which combine probiotics and prebiotics, are currently being evaluated in early-stage cohorts for Parkinson’s disease and Alzheimer’s disease to assess improvements in gut motility and cognitive markers.^{51–53} A major hurdle remains that responses are highly strain-specific and host-dependent, suggesting that future efficacy will rely on personalization guided by baseline microbiota profiling.⁵⁴

4.2. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) represents the most direct method of ecosystem restoration. Currently, it is clinically approved and highly effective for treating recurrent *Clostridioides difficile* infection.⁵⁵ Beyond this indication, FMT is considered experimental. Preclinical studies have shown that transplanting microbiota from healthy donors into Alzheimer’s disease mouse models reduces amyloid plaque load and neuroinflammation, whereas FMT from patients with Parkinson’s disease can induce motor symptoms in healthy mice.^{56,57}

In human immunotherapy, pilot studies in multiple sclerosis and Parkinson’s disease have reported possible

improvements in motor function and fatigue. However, these are largely small, open-label, or phase I/II safety trials. The long-term safety profile regarding the transfer of multi-drug resistant organisms or the unintentional induction of adverse immune phenotypes remains a critical regulatory concern.⁵⁸

4.3. Dietary interventions

Unlike FMT, dietary modulation offers a low-risk, accessible intervention. Observational data strongly support the Mediterranean diet—high in plant fiber and polyphenols—for increasing microbial diversity and anti-inflammatory immune profiles.^{58,59} Conversely, high-fat, low-fiber Western diets promote endotoxemia via LPS leakage, driving chronic low-grade inflammation. Intermittent fasting is also emerging as a modulator of the axis; animal models suggest that it shifts the microbiota toward SCFA-producing taxa and improves blood–brain barrier integrity, though human clinical data on this specific mechanism are limited.⁶⁰

4.4. Next-generation therapeutics

The field is moving toward precision medicine with “next-gen” therapeutics. Postbiotics, nonviable bacterial products such as SCFAs or exopolysaccharides, offer

immune-modulating benefits with a more favorable safety profile than live organisms. Furthermore, synthetic biology enables the creation of engineered strains of *Escherichia coli* and *Bacteroides* that secrete neuroprotective molecules or degrade pro-inflammatory mediators. Phage therapy is also being revisited as a tool to precisely excise pathogenic strains while sparing the beneficial community. Finally, small-molecule mimetics of microbial metabolites are under active investigation in preclinical models for their ability to dampen microglial activation.^{61,62}

5. Clinical and translational implications of developmental symbiosis

Clinical and translational implications of developmental symbiosis are summarized in [Table 3](#).

6. Future directions

6.1. Toward precision developmental immunology

The concept of developmental symbiosis has transitioned from a theoretical construct to a translational target.

Table 3. Clinical and translational implications of developmental symbiosis

Intervention area	Strategy	Target window	Rationale	Emerging evidence	Key references
Maternal microbiome optimization	Dietary fiber, probiotics, antibiotic stewardship	Preconception and pregnancy	Shapes fetal immune tolerance, reduces allergy/ autoimmunity risk	Pilot trials show reduced atopy in offspring	20–23
Microbial restoration after birth	Human milk oligosaccharides, probiotics, breast milk feeding, neonatal FMT (experimental)	Neonatal	Corrects early dysbiosis (e.g., C-section, antibiotics)	Small trials show restoration of <i>Bifidobacterium</i> and improved Treg induction	24–30
Childhood probiotic/prebiotic supplementation	Targeted consortia, synbiotics	Early childhood	Enhances immune maturation; prevents atopic diseases	Evidence mixed; more personalized approaches needed	36–39
Environmental microbial reintroduction	Structured exposure to soil/ environmental microbes	Infancy–childhood	Counters “hygiene hypothesis”; broadens immune education	Observational data from farm studies; trials ongoing	40–43
Precision microbiome medicine	Multimics-guided microbial/ immune monitoring; individualized therapy	All stages	Tailors interventions based on host and microbiome profile	Computational models and pilot clinical panels emerging	45–50
Healthy aging strategies	Prebiotic/probiotic supplementation; SCFA restoration	Aging	Reduces inflammaging; enhances vaccine responses	Initial evidence of improved cognition and immune tone	51–54

Abbreviations: FMT: Fecal microbiota transplantation; SCFA: Short-chain fatty acid; Treg: Regulatory T cell.

However, the inconsistency of clinical trial results highlights the need for precision microbiota modulation. Future interventions must be tailored to individual parameters, including age, host genetics, and baseline immune phenotype. The integration of multimics (metagenomics, metabolomics, immunophenotyping) into clinical algorithms could allow practitioners to identify the optimal “window of opportunity” for intervention, whether it be maternal dietary optimization during pregnancy or targeted restoration following antibiotic exposure in the elderly.

6.2. Restoring the symbiotic partnership

Strategies focused on the maternal–fetal interface are gaining traction. Evidence suggests that optimizing the maternal microbiome via diet and antibiotic stewardship

may preemptively enhance offspring immune resilience. Similarly, “microbial restoration protocols” for neonates born via C-section (e.g., vaginal seeding or defined consortia) are under investigation, though they require rigorous safety validation before clinical adoption.

Addressing the “Hygiene Hypothesis” (or “Old Friends” depletion) may ultimately require reintroducing lost microbial exposures. Interventional studies are exploring whether structured exposure to environmental biodiversity or next-generation probiotics mimicking ancestral strains can recalibrate immune tolerance in urbanized populations.

7. Conclusion

The immune system is not a self-contained entity but a

co-evolved system reliant on its microbial partners for proper maturation and function. This review outlines the chronological arc of this partnership, from the metabolic priming of the prenatal period to the immunosenescence of aging. The evidence underscores that the earliest years of life, and to a lesser extent, adolescence, represent distinct periods of immunological plasticity where microbial signals exert a disproportionate and lasting influence.

Recognizing the microbiome as an active architect of immunity offers a paradigm shift for medicine. The challenge for the next decade is to move beyond description to prescription, developing safe, stage-specific interventions that preserve or restore this vital evolutionary alliance. With sustained investment in longitudinal studies and precision therapeutics, the principles of developmental symbiosis could transform the prevention and management of immune-mediated diseases in the 21st century.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Visualization: All authors

Writing—original draft: All authors

Writing—review & editing: All authors

Ethical approval and consent to participate

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