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Microbiome and Vaccine Response: Evidence Synthesis

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ABSTRACT

The human microbiome, particularly the gut microbiota, plays a central role in shaping immune development, homeostasis, and function. Increasing evidence suggests that inter-individual variation in microbial composition and diversity may influence vaccine responses, potentially accounting for disparities in immunogenicity across populations and age groups. Animal models have demonstrated that microbial molecules act as natural adjuvants, modulating innate and adaptive immune pathways critical for effective immunization. Human clinical and observational studies, though heterogeneous and often inconclusive, indicate associations between microbiome composition, vaccine-induced antibody responses, and adverse effects. Specific vaccines including influenza, COVID-19, and pediatric immunizations have shown variable outcomes linked to gut microbial diversity, metabolites such as short-chain fatty acids, and immunomodulatory taxa. Interventions with probiotics, prebiotics, and dietary strategies have yielded mixed results but remain promising approaches for enhancing vaccine efficacy. Methodological challenges, population variability, and ethical considerations complicate the translation of microbiome research into actionable vaccination strategies. Future directions emphasize longitudinal, multi-omics studies, systems vaccinology, and personalized approaches integrating microbiome profiling into vaccine development and policy. A deeper understanding of microbiota–immune interactions holds the potential to optimize immunization outcomes and strengthen public health programs globally.

Keywords: Microbiome**,** Vaccine Response**,** Immunogenicity, Gut Microbiota**,** Probiotics and Immunity.

INTRODUCTION

A microbiome is the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space [1]. The human microbiota varies between individuals, populations, geographic locations, and diets, yet remains fairly stable over time. The human microbiota contains many more genes than the host, expanding the metabolic capacity and processes available to the individual. Most of the microbiota resides in the gut providing access to diet-derived nutrients and being in contact with the intestinal mucosa, which is a major barrier to the outside world [2]. This biogeographical location makes the microbiota and its metabolism accessible to the host, in particular to the immune system. The immune system is activated at birth and undergoes a maturation process until adolescence, when it becomes relatively stable. This maturation and resting state is largely influenced by the interaction with the microbiota. During adulthood, the immune system faces many "disturbances" such as diet, pregnancy, or infections, creating causes of oscillations that over time make the immune system and microbial community capable of adapting to a new stable state, i.e., resilient. Because most of the communication between the microbiota and the host occurs through the immune system, changes in the immune system will affect the composition of the microbiota. The gastrointestinal tract contains the largest reservoir and densest community of microbiota. It is estimated that 40% of small molecules found in human blood originate from microbiota. These molecules span a wide range of chemical classes, extending the accessible molecular diversity. The metabolic landscape of the microbiota depends not only on the composition but also on the diet, which is in constant evolution due to changes in the environment and external conditions. The co-metabolism creates a range of chemical entities that strongly impact physiology, immune responses, autoimmunity, allergy, HIV prevention, and cancer immunotherapy. Evidence of the role of the microbiome in

modulating the response to vaccination remains sparse and somewhat controversial. The majority of evidence comes from mouse studies, whereas cohort and interventional human studies provided both supportive and contradictory results. Immunization strategies in these low- and middle-income countries are of critical importance for public health, yet microbiome modulation of the immune response to vaccination in this setting remains poorly characterized. Antibiotic use in neonates and infants can cause long-lasting alterations in microbiota composition that may differentially alter responses to vaccines administered months later.

Understanding Vaccine Response

Vaccines reliably induce protective immune responses that prevent infections and reduce disease severity in vaccinated individuals. While vaccines incorporate the antigen, commonly a purified protein or inactivated pathogen, many additional host and environmental factors regulate whether vaccination generates a protective immune response [2]. An understanding of these aspects of vaccine immune response is essential for evaluating the evidence on the potential role of the microbiome in modulating vaccine immunity. Regulation of immune responses by vaccines depends on the specific antigen and the subsequent immunological context of the response. Following exposure to an antigen, the immune system elaborates both systemic and mucosal responses broadly driving pathogen neutralization, clearance, and sometimes long-term protective immunity [3]. Antigens themselves may elicit variable innate immune activation that influences local cytokine milieu. Such specific cytokine contexts alter the extent of humoral immune response and determine whether the transition from innate to adaptive immunity promotes limited or durable immunity. This contextual response is critical to the continued elaboration of life-long immune memory, supported by the expansion of circulating memory B and T-cell pools on challenge [1]. Vaccination strategies supporting the development of immunological memory are generally most effective, with the pivotal need to develop a comprehensive understanding of mechanisms regulating this process well recognized.

The Role of the Microbiome in Immune Function

The microbiome is increasingly recognized as a factor influencing human health. This is exemplified by growing evidence indicating that individual variability in microbiome composition might partially account for the variability in vaccine response [2]. A vaccine constitutes an antigenic preparation that, once administered, induces the immune system to produce specific, long-lived, protective responses against a pathogen. Both the development of immune responses and protection following vaccination require a competent immune system capable of appropriate reactiveness [1]. The microbiome performs an important role in human physiology and shapes immune development, homeostasis, and function [3].

Microbiome Composition and Diversity

The human microbiome encompasses distinct microbial communities residing in various anatomical sites on and within the human body. The microbial variation within these communities depends on the sampled site, duration of exposure to external microbes, the individual's genetics, and early-life colonization events. The gut microbiome, extensively studied in relation to vaccine response due to its accessibility and substantial biomass, exhibits significant variations among individuals and populations [2]. Factors such as geographical location, diet, age, and health status influence gut microbial composition. Notably, low- and middle-income countries introduce early-life environmental pressures that diverge from high-income countries, particularly with extensive antibiotic use in neonates and infants leading to long-term microbiota alterations that can affect vaccine immune responses [2].

Factors Influencing Microbiome Diversity

Multiple non-genetic factors influence the composition and dynamics of the human microbiota, producing qualitatively and quantitatively heterogeneous microbial populations among individuals. The microbiota varies considerably in terms of the different species and strains of bacteria present, while the proportions and amounts of these species and strains can also differ substantially. These key parameters are affected by genetic and non-genetic factors, including age, geographical area, and diet [1]. Nonetheless, environmental exposures have the greatest impact on the gut microbiota throughout life. For example, during the early postnatal period, delivery mode is associated with major differences in gut microbial composition: vaginally born infants acquire a microbiota resembling their mother's vaginal microbiota, while infants born by caesarean section acquire a microbiota dominated by environmental bacteria. Passive and active smoking and alcohol consumption affect the respiratory and intestinal microbiotas. A strong relationship is also observed between lifestyle, diet and oral, intestinal, and possibly respiratory microbiotas. The impact of dietary habits on the composition of the gut microbiota is numerous and fine-tuned. For instance, Mediterranean, gluten- or rich-protein diets can significantly change the structure of the microbiota by driving a modification of the microbial species or strains present. Batterink et al. revealed that the microbe genus Bifidobacterium is associated with habitual consumption of whole grains as a primary predictor of healthy grain consumption [2]. Symbiotic modulation of microbial populations can also be

achieved through the administration of probiotics and prebiotics. Finally, antibiotic consumption, even a single dose, rapidly leads to profound changes in the intestinal microbial community, perturbations which may last for years [1, 2].

Methods for Assessing Microbiome Composition

Understanding the microbiome composition is essential for interpreting its role in vaccine response. Advances in sequencing technologies have facilitated large-scale investigation of microbiome compositions across body sites and temporal scales [2]. The most commonly used method is 16S ribosomal RNA sequencing, targeting hypervariable regions of the universally conserved 16S rRNA gene. Next-generation sequencing enables the study of this gene at a greater depth and resolution than was previously possible. The collection of sequence reads is processed into operational taxonomic units (OTUs) that are representative of the phylotypes present in a microbiota sample. 16S rRNA sequencing is accurate at discriminating bacteria at the genus level; however, it is less suitable for species or strain-level delineations. More comprehensive methods, such as metagenomic and metatranscriptomic shotgun sequencing, capture all DNA and RNA in a microbial population [2, 1].

Impact of Microbiome on Vaccine Efficacy

Vaccines constitute an efficient and cost-effective approach to preventing infectious diseases. They engage both innate and adaptive immunity to generate immune memory of the encounter with a given pathogen, leading to protection against infection. However, responses to vaccines vary widely among individuals [1]. Understanding the mechanisms responsible for vaccine variation provides the potential to improve immunization strategies and effectiveness, particularly in endemic areas where greater variability exists. Variations in vaccine responses can arise as a consequence of intrinsic host factors (e.g., age, sex, genetics), extrinsic factors (e.g., preexisting immunity, microbial infections), perinatal factors (e.g., mode of delivery, breastfeeding, environmental exposure), and behavioral factors (e.g., diet, smoking, exercise). Current evidence indicates a close relationship between the microbiota, the immune system, and vaccine responses [2]. The microbiota can affect vaccine responses by acting as an immunologic modulator, natural vaccine adjuvant, or cross-reactive antigen. Given its pivotal role in shaping host immunity, understanding the microbiome in the context of vaccination offers new opportunities to increase vaccine efficacy [1].

Evidence from Animal Studies

Preclinical data in germ-free and antibiotic-treated animal models demonstrated multifactorial microbial control of the generation of systemic immunity to vaccination. Studies with Gram-negative bacterial adjuvants revealed major roles for specific microbial molecules in the early innate adjuvant effects of the microbiota. Associations between vaccine immunogenicity and microbial abundances in clinical studies have been interpreted using animal models. Germ-free and antibiotics-treated animals may have direct effects on immunity unrelated to changes in microbiota [4]. In mice, diverse microbial system members controlled the generation of pathogen-specific systemic immunity to the inactivated influenza vaccine. For example, muscle injection of haemagglutinin and neuraminidase from influenza did not stimulate Toll-like receptor (TLR) signalling and elicited substantially lower haemagglutination inhibition and influenza-specific IgG, IgG1, and IgG2c titres in germ-free and antibiotics-treated mice than in conventionally raised mice. Provision of flagellin (a TLR5 agonist) and other TLR agonists restored haemagglutination inhibition titres to the same degree as the wild-type cecal microbiota. Stimulation of germinal centre B-cell formation, activation-induced cytidine deaminase (AID) expression, and plasma-cell differentiation after influenza vaccination was also impaired. Three days after subcutaneous injection, defective expression of a subset of immune genes was observed in lymph nodes from antibiotic-treated mice, including genes involved in antigen presentation, dendritic cell (DC) recruitment, and lymphocyte homing. Haemagglutination inhibition titres elicited by intramuscular injection of the adjuvanted seasonal influenza vaccine were not decreased in antibiotics-treated mice. Mice lacking the inflammasome component NLRP3 were defective in response to adjuvanted, but not unadjuvanted, vaccines [4].

Human Clinical Trials and Observational Studies

Outcome measures in clinical trials include B-cell, T-cell, and cytokine responses on systemic and mucosal sites, plus adverse events such as gastrointestinal and respiratory tract infections [1]. The literature search yielded 34 human studies published in the past 15 years, of which 18 were randomized controlled trials and 16 observational designs that evaluated the role of either probiotics or the gut microbiome on vaccine response. Projection of the microbiome is useful for the prediction of antibody response induced by influenza and oral rotavirus vaccines [1].

Mechanisms of Microbiome Influence on Immune Response

The human microbiome contains thousands of species of microbes with a total genome that far exceeds our own. Specific microbes and their biologically active gene products have evolved to shape human physiology and regulate immune responses [1]. Microbiota influences the development and modulation of immune function, and a range of

bioactive molecules directly link the microbiota to immunomodulation. These molecules include dietary products transformed by the microbiota (such as short-chain fatty acids), metabolites produced de novo (such as sphingolipids), and bacteria-derived components (such as flagellin or capsular polysaccharides) that interact with innate immune receptors [2]. Living organisms also express antigens and cross-reactive epitopes that can directly engage the adaptive immune system to establish memory.

Metabolites and Immune Modulation

Microorganisms have evolved to shape or subvert mammalian immune function by expressing immune-modulatory molecules. Metabolites shaped by or derived from microbiota thus control host inflammatory responses at the respiratory, gastrointestinal, and dermal mucosae and bile composition, and exposure to antibiotics leads to exaggerated pathologic immune responses upon viral respiratory infection [1]. Bile acid derivatives, the products of both host and microbial metabolism, modulate type 3 ILC and T_H17 development in the small intestine and regulate T_H17 and regulatory T cell axis in the colon [2]. Microbiota-derived short-chain fatty acids modulate macrophage, DC, and neutrophil function as well as B and T cell responses. These metabolites act through host G protein-coupled receptors, affecting intracellular signalling cascades. A wide array of microbiota-produced tryptophan metabolites influences intestinal epithelial and innate immune cells through the aryl hydrocarbon receptor. Peptidoglycan primes systemic innate immunity to bacterial infection. Trained innate immune memory can be mediated by microbial metabolites, and microbiota composition affects the hematopoietic progenitors producing mono- and granulocytes. Mediators such as prostaglandin-E2 modulate innate immunity and can inhibit the development of memory CD8^+ and CD4^+ T cells. Microbiota-derived signals influence haematopoiesis and basophil haematopoiesis, differentiation, and activation [1, 2].

Microbial Antigens and Immune Training

The microbiota constitutes a substantial source of microbial antigens that activate pattern-recognition receptors, initiating a complex immune response that may ultimately enhance or attenuate subsequent pulsatile responses [1]. The recognition of microbially derived antigens by pattern-recognition receptors expressed on innate immune cells and epithelial cells triggers signalling cascades that influence memory B-cell responses and promote immunoglobulin A (IgA) class switching. In particular, Bacteroides fragilis has been explicitly shown to promote intestinal IgA production; synergistically, bacterial flagellins also induce IgA, although they remain targets of these antibodies. In the intestinal lumen, induction of IgA expression by commensal organisms is mediated through dendritic cells, which can induce a diversified IgA repertoire even in the absence of direct microbial sensing by B cells. Although the discussion has primarily centred on the gut microbiota, it is important to consider that microbial communities in the upper airways and oral cavity also have the capacity to influence systemic immunity and vaccine responsiveness [1].

Microbiome and Specific Vaccines

The composition of an individual's microbiome has been implicated in efficacies elicited by influenza, COVID-19, and widely administered pediatric vaccines [1]. The gut microbiome influences influenza vaccine immunogenicity in both adults and infants, an effect that can be reversed by broad-spectrum antibiotics. Differential microbiome composition modulates Toll-like receptor 5 (TLR5) ligands and subsequent B cell responses. The respiratory mucosal microbiome may play a role in nasal vaccination models [2]. Conversely, protracted antibiotic treatment enhances rotavirus vaccine immunogenicity by sustaining prolonged changes in host microbial communities.

Influenza Vaccine

Prophylaxis against influenza involves multivalent vaccines targeting predicted circulating viral strains and antiviral drugs approved for therapy; nonetheless, influenza-associated morbidity and mortality globally remain substantial [1]. Influenza vaccine effectiveness varies with strain and vaccine match to circulating variants. The microbiome has been reported to influence responses to various influenza vaccination types. Murine influenza vaccination has been employed to investigate microbial species that enhance vaccine-induced immunity and to characterize the mechanisms involved. Antibiotic treatment and microbiome depletion, as well as GF murine models, establish the gut microorganisms for antibody accumulation post-influenza vaccination [4]. Although the intestinal and respiratory tracts are distal compartments, overlap exists in prescription patterns affecting microbiota composition. Antibiotic treatment prior to Spn colonization elevates pulmonary pneumococcal density in human subjects, resulting in decreased cellular and humoral immune responses, including impaired influenza vaccination outcomes. Subjects exhibiting optimal innate, Tfh, and B-cell responses to the trivalent inactivated influenza vaccine (TIV) display more diverse gut microbiomes than non-responders. Enhanced responses are associated with increased gene richness and elevated abundances of MeHMI and Prevotella copri. Replenishment of SCFAs, resulting from the colonization of mice with a bacterial consortium isolated from the feces of subjects exhibiting high levels of MeHMI, leads to heightened immune gene expression in Peyer's patches and bone

marrow; these effects are attenuated in GPR43−/− mice, indicating that the modulation of systemic immunity by the gut microbiota and SCFAs is dependent on GPR43 receptors. Acetate supplementation augments the generation of class-switched antibodies by upregulating Aicda and Xbp1 transcripts in vitro, suggesting a potential mechanism through which SCFAs influence antibody responses. Colonization with the commensals Streptococcus gallolyticus, S. salivarius, Propionibacterium acnes, and Staphylococcus aureus prior to influenza vaccination in antibiotic-treated mice variables the expression of gene sets associated with energy metabolism and B-cell proliferation in Peyer's patches and mesenteric lymph nodes. These experimental analyses associate certain bacterial taxa with the alteration of specific immune pathways related to vaccine responsiveness [4].

COVID-19 Vaccine

Correlation between gut microbiome and COVID-19 infection has inspired investigations of a possible connection between microbiota and vaccination immunogenicity [5]. Animal models revealed that antibiotics-induced dysbiosis decreased the immunogenicity of COVID-19 vaccines. Enrichment of immunomodulatory bacteria such as Bifidobacterium choerinum is positively associated with neutralizing antibody titers in adult vaccine recipients. Baseline gut microbiota, including species involved with immune modulation, correlated with immunogenicity and adverse effects. Pathways related to fatty acid biosynthesis and fermentation to short-chain fatty acids (SCFAs) decreased after vaccination, yet were linked to enhanced immunity. Specific bacteria (Anaerostipes hadrus, Collinsella aerofaciens, and Veillonella dispar) and SCFAs (acetic and butyric acid) were positively associated with antibody levels. Individuals reporting fewer adverse effects exhibited decreased species richness and enrichment of Prevotella copri, consistent with its anti-inflammatory properties [5]. The gut microbiota, particularly immunomodulatory species, thus influence COVID-19 vaccine response and safety. Variability of the gut microbiome between individuals, populations, and across the lifespan affects vaccination outcomes and correlates with age, diet, and chronic conditions. It underlies the regulation of immune responses, including autoimmunity, allergies, HIV infection susceptibility, and cancer immunotherapy effectiveness. Evidence from mouse models supports active contribution of the microbiota to vaccine response; however, clinical studies remain inconclusive, potentially due to differences in studied microbiota components, vaccination protocols, and sample timing [1]. Modulation of vaccine response through microbiome dynamics is particularly relevant in low- and middle-income countries, since antibiotic use induces long-lasting microbial alterations that may impact immunization success. A clear demonstration of microbiota influence on COVID-19 vaccine efficacy has yet to emerge, calling for further investigation [1, 5].

Pediatric Vaccines

Vaccine-induced protection is mediated through innate and adaptive immune responses, but considerable variation limits vaccine effectiveness. A growing body of evidence indicates that the gut microbiota is an important contributor to individual immune variation. In early life, the development of the gut microbiome is determined by mode of delivery and other perinatal factors, which modulate subsequent antigen-specific antibody responses to several pediatric vaccines. These findings provide additional support for the role of the gut microbiota in vaccine immunogenicity and suggest a target for improving vaccine responses in early childhood [6]. Large variation in vaccine-specific antibody responses has raised concern that some infants might remain insufficiently protected. Studies on factors underlying this large variation in early-life vaccine responses led to the gut microbiota as a modifiable target to improve vaccine immunogenicity. Understanding the temporal relation between early-life host- and lifestyle factors, gut microbiota development, and vaccine responses can help guide the timing and design of interventions to support a healthy gut microbiota and improved immunogenicity after vaccination [6].

Microbiome Interventions to Enhance Vaccine Response

Strategies to modulate the microbiome hold potential to enhance vaccine immunogenicity and clinical protection. Probiotics and prebiotics represent common approaches to alter microbial composition, activity, and metabolite production [2]. Clinical studies have assessed whether these agents can augment vaccine responses, with some preclinical evidence supporting immunogenic improvements, though results in human trials remain inconsistent. Dietary interventions also impact microbiome diversity and function, thereby influencing immunomodulation and vaccine outcomes. Investigations into such nutritional strategies have demonstrated effects on microbial communities that may translate to enhanced vaccine efficacy [1]. Continued research is necessary to elucidate optimal means of leveraging microbiome modulation for improved vaccination performance.

Probiotics and Prebiotics

Dietary interventions aimed at modulating the microbiome may enhance vaccine efficacy. Probiotics and prebiotics constitute the most studied interventions in this context. However, although the addition of probiotic strains to the vaccine formulation has been investigated (via recombinant strains and DNA-based delivery systems), limited research has explored the use of probiotics as ancillary agents administered orally alongside vaccines [7].

Probiotic supplementation modifies microbiota composition and diversity. Post-administration shifts in stool microbiome composition have been observed within a few days, accompanied by increased bacterial diversity and more robust vaccine responses. The effect of probiotics on gut barrier function has also been investigated: supplementation promotes the expression of tight junction proteins such as zonulin, occludin, and claudin-1, as well as adhesion molecules like CEACAM1, thereby enhancing gut integrity [7].

Dietary Interventions

Antibiotics, probiotics, and other synthetic and naturopathogenic compounds also substantially influence vaccine responsiveness. When given before immunization or vaccination, they can act either as stimulators or suppressants of the immune response. Dietary interventions support the maintenance of a varied and diversified microbiota, reducing the risk of dysbiosis and suppressing the onset of communicable and noncommunicable diseases [1]. Several clinical trials have analyzed the effect of various interventions based on probiotics, prebiotics, synbiotics, or dietary supplements on the response to vaccines against influenza, COVID-19, and other infectious diseases. Although there appears to be an effect, the results have been inconclusive, with the potential benefit generally being more evident in the case of underdeveloped or weakened immune systems [4].

Challenges in Researching Microbiome and Vaccine Response

Understanding how the microbiome influences vaccine efficacy holds potential for improving vaccine design and implementation. However, challenges remain in elucidating microbiome-dependent mechanisms underpinning immune response [3, 1]. Large variability often characterizes available results, limiting their interpretation and their translation into actionable strategies for enhancing vaccine immunogenicity. Outstanding issues arise from the heterogeneity of available research approaches and study methodologies. Additional challenges stem from the need to model microbiome-immune interactions leading to clinically relevant modulation, while incorporating geographic, socioeconomic, and genetic diversity. Meeting these challenges is fundamental for clarifying causal relationships, defining molecular mechanisms, and advancing microbially derived immunomodulatory strategies with therapeutic promise [3, 1].

Variability in Microbiome Studies

Microbiome variability is a substantial challenge in studies examining its impact on vaccine response [1]. The gut microbiota varies considerably between individuals, populations, geographic locations, and diets. This variability contributes to inconsistencies in immunization outcomes such as seroconversion rates and antibody titres. Evidence from clinical studies is often conflicting, and results from one population may not be generalizable to others. Even asymptomatic carriage of pathogens can influence vaccine efficacy. This variability suggests that large, randomized, controlled vaccination cohorts will be necessary to adequately assess the microbiome's role in immunity [1].

Ethical Considerations

The study of the human microbiome entails a careful approach to the ethics of scientific discovery and to the ethical challenges that might arise as analysis and clinical applications of knowledge develop [1]. Hence, the scientific task of characterizing the microbiome entails explicit attention to the ethical considerations of that research. Ethics apply globally, but the geographical distribution of those infected by the virus can help account for the geographical distribution of the microRNA types associated with the virus [1]. The World Health Organization (WHO) prioritizes vaccines that are safe, effective, affordable, and target local needs, with the regulatory process varying by country. Because each pathogenic threat develops and progresses differently, the study and development of vaccines constitutes a dynamic, high-stakes challenge with significant ethical consequences [1].

Future Directions in Microbiome and Vaccine Research

A better understanding of the microbiome-immune interaction and the influence of the microbiome on vaccine response is needed. Moving from correlation to causation necessitates defining clinically relevant, microbiota-dependent immunomodulatory mechanisms. Improvement areas include designing interventional studies focused on early life across diverse populations, applying systems vaccinology approaches to dissect microbiota-immune response interactions, and identifying immunomodulatory taxa of clinical relevance to establish causality and elucidate mechanisms with model systems. These advances have the potential to reveal signatures and pathways that enable microbial immune-enhancing interventions for general health and vaccination [1]. Vaccine efficacy is influenced by the immune system's ability to respond to antigens, and recent evidence indicates that the microbiota can modulate immune responses and act as a natural vaccine adjuvant. During early life, the gut microbiota shapes immunologic functions, and its composition may explain regional differences in vaccine responses. Environmental, socioeconomic, nutritional, and hygiene factors affect microbiota composition, potentially contributing to vaccine non-response in some populations. Specific bacterial species or components can modulate immunity among vaccine

responders. Probiotic interventions aimed at enhancing vaccine responses have yielded mixed results. Ongoing research is required to elucidate the microbiota's role in vaccine immunogenicity and to develop microbiota-based strategies for improving vaccine efficacy [2]. Current challenges in investigating the microbiota's role in vaccine immune responses include the need for robust tools such as metagenomics, metatranscriptomics, and systems biology approaches. Although reliable animal models with defined microbial compositions, such as gnotobiotic mice, have provided valuable insights, they do not fully replicate natural microbiota complexity. Human studies are complicated by inter-individual variability, genetic diversity, and population-level differences in microbiota. Modifying the microbiota with antibiotics to assess effects on vaccine response presents potential, yet has limitations. The interaction between early microbiome development and vaccination, especially in infants and children, remains insufficiently explored. Most clinical studies to date establish correlations, not causality, between microbiome characteristics and vaccine immunogenicity or efficacy [3].

Personalized Vaccination Strategies

Personalized vaccination strategies recognize the inherent variability in vaccine-induced immune responses across individuals and populations, underscoring an approach tailored to individual characteristics to enhance efficacy. Integrating factors such as the composition of the human microbiome into vaccination protocols aims to maximize immune protection [1]. The microbiome has emerged as a promising contributor to protective immunity in response to vaccination, suggesting that braiding its consideration into future vaccine development could offer a pathway toward optimizing vaccine effectiveness. While evidence of the microbiome's role in vaccine immunogenicity is compelling, some studies present inconsistent findings that necessitate careful elaboration and further scrutiny to resolve uncertainties and refine personalized approaches [1]. A comprehensive understanding of these relationships, coupled with strategies to modulate the microbiota, holds the potential to inform the design of vaccines with enhanced immunogenic profiles and transcends existing considerations to guide the evolution of next-generation vaccines [2].

Longitudinal Studies and Data Integration

The microbiome–vaccine relationship is profoundly dynamic and shaped by the host immune state as well as the microbiome itself. Microbial colonisation begins immediately after birth, and through early life the highly plastic microbiome evolves into a more stable adult-type configuration. This process parallels immune system development, and longitudinal surveys enable exploration of how age-dependent changes influence vaccine immunity [1]. Such studies thus address the chicken-and-egg problem of whether the microbiome modulates host immunity or vice versa. For example, investigations of adult twins in the Human Microbiome Project (HMP) found that Fas ligand (FasL) expression regulated the Firmicutes–Bacteroidetes ratio in the gut, indicating immune control of the microbiota. An analysis of 43 Bangladeshi infants revealed that increased asymptomatic enteric infections were associated with impaired oral polio vaccine seroconversion and a more dysbiotic bacterial community. However, despite accounting for concurrent infection, no significant relation between microbiome composition and oral polio vaccine response was observed. Another study of 3–5year-old Bangladeshi children receiving an oral live-attenuated rotavirus vaccine (Rotarix) identified novel strain-specific IgA correlates of protection, with vaccination partly restoring the collapse of PR8-reactive B cells associated with protection following natural infection. Integrating vaccine response data with longitudinal microbiome data using multivariate statistical methods such as sparse generalized canonical correlation analysis (sGCCA) can unveil underlying relationships [1, 8]. Systems vaccinology approaches provide the resolution and scope to unravel the dynamic microbiome–immunity relationship and identify robust correlates of protection. Longitudinal profiling, including transcriptomics, proteomics, metabolomics, and immunophenotyping of paired vaccine and microbiome samples, followed by simultaneous integration and modelling, enables correlation of systemic responses with vaccine outcome or microbiome composition. Vaccine-induced changes in the microbiome over time can be tracked alongside immune status, generating mechanistic hypotheses and advancing understanding of the interplay between the microbiome and vaccine response [1, 9].

Policy Implications of Microbiome Research

The microbiome can substantially influence vaccine outcomes and, consequently, may inform vaccine development processes and the design of immunization programs [1, 10]. Therefore, vaccine development guidelines should integrate a preliminary assessment of the microbiome, followed by criteria for optimizing microbiome composition during subsequent clinical trials [2, 11]. Similarly, public health policies could consider the microbiome in the formulation of cultural recommendations to enhance vaccine effectiveness, exemplified by the increased responsiveness to the COVID-19 vaccine associated with improved gut microbiome composition.

Guidelines for Vaccine Development

The emerging evidence for the influence of the human microbiota on vaccine responses presents new opportunities to optimize vaccine development. During preclinical vaccine assessment, a perturbed or compromised microbiota may result in underestimation of vaccine efficacy and altered safety profiles, while restoration of the microbiota may further improve efficacy. Moreover, microbiota-vaccine response studies are not usual considerations during regulatory approval, yet adverse reactions and suboptimal responses linked to the microbiota are clinically impactful [1, 12]. As such, deeper knowledge of the effect of vaccine delivery on the resident microbiota is also important. Immune responses to vaccination may protect against disease, but they may also, in part, explain the fluctuations of some chronic conditions. Of key importance, the current animal models in which vaccine efficacy is established often do not reflect either the early-life human microbiome, which plays a key role in immune development, or the steady-state microbiome in populations that experience the majority of vaccine-preventable childhood infections. Findings from the first clinical trials incorporating the microbiota highlight the potentially beneficial effects of probiotics on vaccine immunogenicity. Countries, such as the UK, which are now recommending probiotics for COVID-19 should continue to collect epidemiological data associated with vaccine response. The potential exists for a probiotic strategy to confer earlier protection and to assist vaccine responses for those in whom optimal vaccine efficacy is less likely, such as the immunocompromised and immunosenescent [13].

Public Health Recommendations

The microbiome refers to the communities of microbes, including their genes and metabolites that inhabit the human body [1]. The microbiota harbours a collection of microorganisms composed of bacteria, archaea, viruses, fungi, and protozoa, with the gut microbiota remaining the most characterised microbial community in humans. The gut microbiota has been reported to encode up to 4·5 million non-redundant genes, a genetic repertoire 150-fold larger than the entire human genome. These microbial communities are involved in digestion, providing key metabolic functions (including short-chain fatty acids), supporting the immune system, preventing pathogen colonisation and shaping behaviour. Consequently, the microbiota is implicated in breaking down food components such as oligosaccharides, carbohydrates, peptides, and xenobiotics, regulating nutrient absorption and subsequently energy storage by the host. The microbiota contributes to the establishment and training of the immune system and can promote health by blocking opportunistic pathogens (e.g., Clostridium difficile) through competitive exclusion and immune responses [1]. Humans harbour between 10^13 and 10^14 microbes in the gut alone, with the microbiota varying between individuals, across populations, and throughout life. Factors such as early-life environment, mode of birth, feeding method, diet, lifestyle, vaccination status, medication, infection, and geographical differences shape colonisation and consequently the development of the microbiota. The gut microbiota composition undergoes significant changes during infancy and adulthood, eventually reaching adult-like levels of diversity by 3 years of age. The progressive colonisation and maturation of the microbiota community throughout infancy supports the development of the immune system comprising a complex network of cells, tissues, organs, and mediators. It encompasses the regulation of immune responses, balance between pro- and anti-inflammatory responses, immune development, the establishment of immune tolerance, and the calibration of immunological memory [14].

CONCLUSION

The microbiome is increasingly recognized as a determinant of vaccine responsiveness, shaping both innate and adaptive immunity through microbial metabolites, antigens, and cross-reactive epitopes. Evidence from animal models highlights the mechanistic basis of microbial influence on immunogenicity, while human studies underscore variability across populations, vaccines, and life stages. Although results are not yet consistent, the microbiome presents a promising target for improving vaccine efficacy, particularly in vulnerable populations and low- and middle-income countries where variability in vaccine response remains a critical challenge. Emerging strategies, including microbiota modulation with probiotics, prebiotics, and dietary interventions, offer opportunities to enhance immunization outcomes but require rigorous validation through well-designed clinical trials. Moving forward, integrating microbiome assessment into vaccine development, systems vaccinology, and public health policies will be essential for advancing personalized vaccination strategies. By bridging experimental evidence with clinical application, microbiome research holds transformative potential for next-generation vaccines and for maximizing the benefits of immunization programs worldwide.

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