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MICROBIOME'S INFLUENCE ON EFFICACY OF COVID-19 VACCINES

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Abstract – With the ongoing COVID-19 pandemic, many healthcare workers as well as scientists are pressured by external expectations to find effective approaches that would prevent the spread of the virus within a short period of time including, possible cures, different types of prevention and vaccines. Indeed, the vaccines may have been produced within an appropriate amount of time during the pandemic. However, throughout the processes taken in preventing the spread of the virus, many steps were overlooked. Thus, the efficacy of these vaccines is not at their fullest potential. Here, we discuss a hypothesis emerging from the studies below, regarding the human microbiome influence on the overall efficacy of COVID-19 vaccines. The microbiota's crucial role in modulating vaccine immune responses is further explained through other immune processes that require the help of the microbiota as well as factors that help strengthen or weaken the relationship between the human immune responses and the microbiota itself.

Keywords: Microbiota, COVID-19 Vaccines, Vaccine Efficacy, Immune responses.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronavirus which led to the on-going COVID-19 global pandemic[1]. This newly discovered viral strain threw the current medical world off balance; with no specific antiviral medicines to tackle this infection, vaccines have become the most effective approach in preventing the spread of virus and potentially leading to the eventual end of the ongoing pandemic[2]. Currently, multiple COVID-19 vaccines are in development under numerous ongoing studies[2,3]. These vaccines were approved for immediate use worldwide due to the emergent situation[3]. However, the COVID-19 vaccines are still in the preclinical stages due to the rushed process in mass producing them for the pandemic[3]. While the applications of these vaccines greatly reduce the number of new cases among vaccinated populations, reducing the adverse effects from the vaccines as well as improving the overall efficacy still remains as an issue which requires immediate attention[4].

In recent years, many studies[5] have shown data which supports the concept of how microbes within the human body play a crucial role in the modulation of vaccine immune responses. These studies[5] implicate that the human microbiota governs our body's response to vaccinations as well as the efficacy of the vaccines. Through the alterations of these microbes, a human's response to vaccines will be influenced. However, to understand how the human microbiota interacts with the immune system, as well as how it relates to the modulation of COVID-19 vaccine immune responses, the concept of how microbiota and the immune system are co-dependent must be fully grasped[6].

In this narrative review, we discuss the immune responses to SARS-CoV-2, how COVID-19 vaccines elicit protective immune responses, gut dysbiosis involvement in inefficacy and adverse effects of COVID-19 vaccines and the modulation of the gut microbiota by functional foods to improve COVID-19 vaccine immunizations.

Possible Influences of The Human Microbiota on the Immune Response Vaccination

The mechanism behind immune responses to vaccination is relatively intricate as there are many crucial factors involved in the mechanism, including the host's immune system, possible components related to the vaccines and the gut microbiota[7,8]. In terms of the vaccine itself, there are a number of factors which should be considered, such as the nature of the antigens (i.e., polysaccharide, nucleic acid, microorganism and purified proteins), vaccine formation (i.e., adjuvants, vaccine delivery system, and immunomodulators), route of immunization (parental or mucosal), the dosage, as well as the vaccination schedule[8,9]. Elucidating on the types of vaccination schedules, there are multiple types of vaccination including, intervals between doses, heterologous and homologous prime-boost strategies[10,11]. The listed factors above play a crucial role in shaping the human immune system, as well as evoking optimal responses for specific types of pathogens.

Subsequently, the host's immune system also influences vaccine immune responses predominantly when in the presence of extremes of life such as, age-associated immune alterations, and early life immaturity[5,8]. For instance, among elders, the efficacy of vaccinations are significantly reduced when compared to young adults since countless essential immunological components have declined while other components that potentially lead to inflammation have considerably increased[12]. Furthermore, as mentioned earlier, the gut microbiota has a substantial role in affecting vaccine efficacy due to its critical role in the regulation of the immune system[13,14]. However, composition of the gut microbiota can be quite sensitive to various factors namely, environmental and socio-economic factors (i.e., diet, age), use of immunosuppressive chemotherapy, chronic infections, probiotic usage, and antibiotic treatments (Figure 1)[12]. In addition, geographical heterogeneity may be considered as another crucial factor that affects the body's immune response towards vaccinations[12]. With geographical heterogeneity, there's variation in microbial communities due to inconsistent socioeconomic, nutritional, environmental and hygiene conditions[5,12].

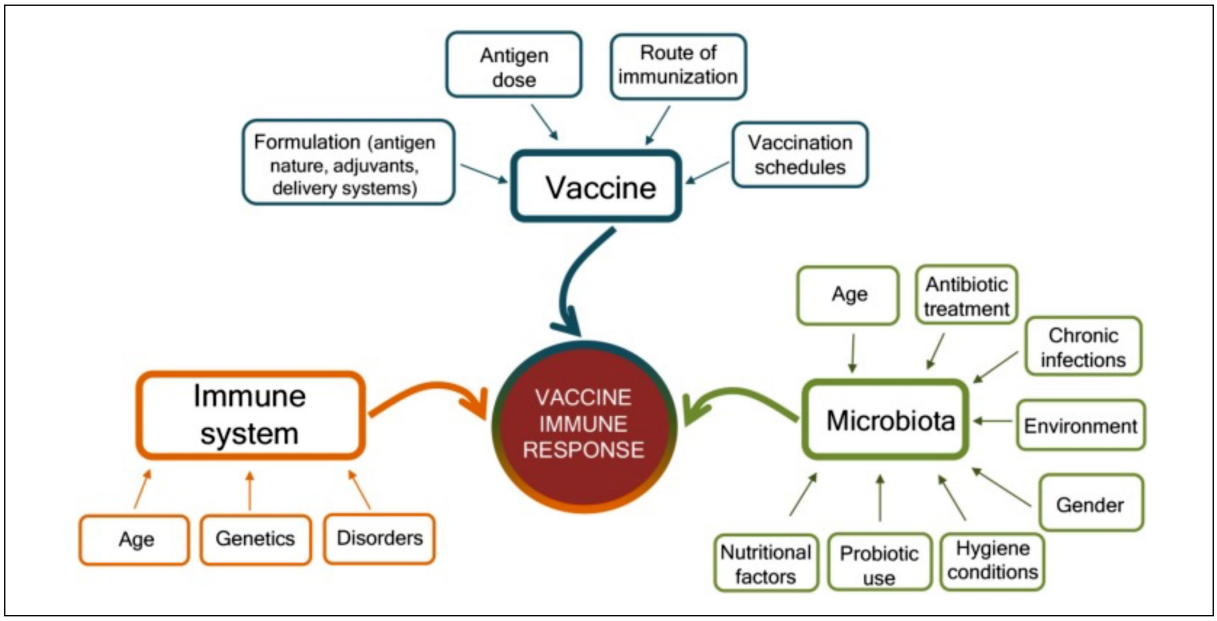

Figure 1. The relationship between immune response and microbiota. In the figure, conditions of the host's gut microbiota are liable to be susceptible to age, environmental and nutritional factors (i.e., gender, probiotic usage, chronic infections, hygiene conditions, etc.). Thus, influencing the capacity of the immune system in response to vaccination[12].

While the specific mechanism which expounds the dependency of immune responses towards vaccination on the human microbiota is still perplexing, there are studies which implicate that microbiota acts as a stable source of natural adjuvants which are substances that enhances immune response when in the presence of antigens[15]. These adjuvants are crucial factors in activating several pathways required in controlling both innate and adaptive immunity[16,17].

Microbiota's potential as a natural adjuvant has been shown in a study which uses inactivated influenza vaccine[18]. The results from the study indicate that antibiotic-treated mice or GF (germ-free) have impaired antibody response towards the vaccines[19]. Suggesting that there is a strong association between TLR5 and the magnitude of antibody responses, TLR5 recognizes innate immune responses[19]. It has been found that the extent of antibody responses among TLR5-deficient mice that were immunized with trivalent inactivated vaccines (TIV) are greatly reduced[19,20]. Through the application of antibiotics treatment on GF mice, we can observe how commensal bacteria acts as the source of TLR5. TLR5 has a key role in enhancing immune responses to TIV[21]. Similar results from the above treatment can be observed from inactivated poliovirus vaccines[22]. Additionally, during the process of oral reconstitution, it is discernible that in order to restore normal antibody responses the flagellated strain of *Escherichia coli* is indispensable[23]. While the flagellated strain is required for this, the results from other vaccines, such as a live attenuated yellow fever vaccine (YF-17D) or an adjuvanted vaccine against tetanus-diphtheria-pertussis have shown that there are other factors which are essential in influencing interactions between the immune system and microbiota as well including, route of immunization, vaccine formulation compositions[12].

Again, although flagellin plays an essential role as a component found in the microbiota, other indispensable components, such as agonists of nucleotide-binding oligomerization domain containing 2 sensors (Nod2) and peptidoglycan component of muramyl dipeptide (MDP) act as an adjuvant which can help enhance the human immune responses to vaccination[24]. For instance, Nod 2 has the ability to enhance immune responses within the nasal cavity in mice to cholera toxin[24]. Similar effects can be seen in the study of Duthie and team in 2011[25]. According to the mentioned study, a specific component known as monophosphoryl lipid A (MPL) which is found in bacterial LPS and can be detected by TLR4, can enhance certain adaptive responses during vaccination[5,15].

Further support can be observed from the result of Lynn et al[8], in which they showed that mice with impaired antibody responses against the five adjuvanted/live vaccines including meningococcal serogroup B vaccine (Bexsero), 13-valent pneumococcal conjugate vaccine (Prevenar), meningococcal serogroup C vaccine (NeisVac-C), hexavalent combination vaccine against hepatitis B, tetanus, diphtheria, pertussis, hemophilus influenzae type B, the tuberculosis BCG vaccine and poliomyelitis virus (INFANRIX Hexa)[20]. During the early life of these mice, an antibiotic-driven dysbiosis occurred. This has been observed in all cases where early exposure to antibiotics lead to an impaired antibody response. Nonetheless, the impairment of these antibody responses was not due to the reduced production of T-cell cytokine since these responses can be restored through commensal microbiota after exposure to antibiotics[14]. On the other hand, adult mice that have been treated with antibiotics did not exhibit any form of impaired responses to the antibodies during vaccination[20]. These observations support the concept of how impairment of humoral responses depend on antibiotic-driven dysbiosis rather than the effects from antibiotics themselves[20].

To fully explore the environmental effects including age, multiple clinical trials were done in order to holistically understand the correlation between vaccine responses in humans with the gut microbiota through comparison between the result of fecal microbiota composition from non-responders and responders among different age groups in high to low income countries[26]. Huda et al[26] investigated the influences of the gut microbiota through the use of systemic vaccines, such as oral polio vaccine (OPV), oral RVV, and cholera among children and infants from lower income countries[26]. The results from the study demonstrated a clear correlation between RVV immunogenicity and microbiome composition by comparing microbiome composition in pre-vaccinated fecal of RVV responders and non-responders in Pakistan and Ghana[27]. It has also been noted that Bacterium related to the *Streptococcus bovis* species were commonly found in Ghanaian responders rather than the non-responders, implicating increase in RVV efficacy[5,27]. However, Prevotella and Bacteroides species were more common

in non-responders, strengthening the observable positive correlation with lack of RVV response[27]. Similar results can be observed from RVV responders in Pakistani infants, showing a correlation with an increase in ratio of Gram-negative bacteria instead of Gram-positive bacteria. Another trend which is demonstrated through the result is the three folds increased in Serratia and *E. coli* in relation to the abundance of Proteobacteria[28]. Additionally, it has been found that within the intestinal microbiota among Dutch infants who have responded with high RVV immune responses, showed an increase in the abundance of Proteobacteria, mainly Gammaproteobacteria including bacteria that are related to *E. coli* and Serratia[27]. As mentioned earlier, these Gram-negative bacteria have the ability to stimulate specific innate immune responses, such as the expression of toxigenic LPS or flagella[5]. This indicates that their cell envelope components have the potential to act as natural immune adjuvants among the Pakistani infants[29]. Through the studies mentioned, we can comprehend the correlations found between RVV immunogenicity and microbiome composition[29]. The results from the studies shown could also be used as an indicator to help us understand different ways to improve vaccine immunogenicity[29].

According to Hill et al[30], when individuals are supplemented with probiotics, the modulation of the human microbiota leads to an improvement in vaccine immunogenicity[30]. This is due to the fact that probiotics are considered as live organisms and, when given at an adequate amount, can be beneficial towards the host[30]. Numerous studies[30] were done to analyze how different probiotic strains modulate the efficacy of different vaccines.

Additionally, Huda et al[26] explored microbiota's role in immune responses to certain parenteral vaccinations among the population of Bangladeshi infants[26]. Focusing on Actinobacteria, the most abundant genera seem to be Bifidobacterium. Some observable positive correlations between adaptive immune responses and Bifidobacterium include delayed-type hypersensitivity to PPD, proliferative responses to PPD and TT of CD4+ and CD8+ T-cell, and specific IgG responses to hepatitis B (HBV) and Tetanus (TT) vaccines[9]. Correspondingly, lower vaccine responses were associated with a copious amount of Enterobacteriales and enteric pathogens or Pseudomonadales (i.e., have the ability to strategically infect and colonize its host)[12,26].

Moreover, during oral reconstitution, it is observable that flagellated strain of *Escherichia coli* was required to restore normal antibody responses[19]. However, other vaccines, including an adjuvanted vaccine against tetanus-diphtheria-pertussis or a live-attenuated yellow fever vaccine (YF-17D), showed that other factors, including vaccine formulation compositions, route of immunization, also influences interactions between the microbiota and immune system[19].

While flagellin plays an important role as a component within the microbiota, there are other components that demonstrate its importance as an adjuvant in order to enhance immune responses to vaccination[24]. Other components, including peptidoglycan component muramyl dipeptide (MDP), agonists of nucleotide-binding oligomerization domain containing 2 (Nod2) sensors have demonstrated their ability to enhance immune responses to cholera toxin within the nasal cavity of mice[24]. Similar results can also be observed, in which a certain component of bacterial LPS that is recognizable to TLR4 called monophosphoryl lipid A (MPL), has the ability to enhance adaptive responses during vaccination[25].

According to Lynn et al[8], the results from their study has shown that if an antibiotic-driven dysbiosis occurs during early life of mice, the mice itself will have impaired antibody responses to these particular five adjuvanted/live vaccines which are frequently used to immunize infants around the world. These include meningococcal serogroup B vaccine (Bexsero); the meningococcal serogroup C vaccine (NeisVac-C); the 13-valent pneumococcal conjugate vaccine (Prevenar); the hexavalent combination vaccine against hepatitis B, diphtheria, tetanus, pertussis, Hemophilus influenzae type b, poliomyelitis virus (INFANRIX Hexa); and the tuberculosis BCG vaccine[20,31]. It has been observed in all cases that early exposure to antibiotics can lead to impaired antibody responses[20]. However, it is not due to the reduced production of T-cell cytokine as these impaired responses are restored through commensal microbiota following antibiotic exposure[20]. In antibiotic-treated adult mice, the mice did not exhibit any observable impaired responses to antibody during vaccination[20] which then supports the concept that impairment of humoral responses is dependent on antibiotic-driven dysbiosis as opposed to the effects from antibiotics themselves[20].

In order to explore environmental effects, as well as age, clinical trials were done in order to understand the correlation between the gut microbiota with vaccine responses in humans by comparing the result of fecal microbiota composition from responders with non-responders in high to low-income countries across different age groups[8]. In Huda et al[26], the influences of the gut microbiota have been investigated through the use of systemic vaccines, mostly oral vaccines including oral RVV, oral polio vaccine (OPV) as well as cholera in infants or children from low-income countries[5,24,26]. The results from Harris et al[27-29] demonstrated a correlation between microbiome composition and RVV immunogenicity through a comparison between pre-vaccinated fecal microbiome composition between RVV responders and non-responders of RVV in Ghana and Pakistan. It is noted that Bacterium related to *Streptococcus bovis* species were common in Ghanaian responders rather than non-responders, increasing RVV efficacy. Bacteroides and Prevotella species, which were more commonly found in non-responders, showed a positive correlation with lack of RVV response[27]. Similarly, RVV responders in Pakistani infants showed a correlation with an increased ratio of Gram-negative bacteria rather than Gram-positive bacteria. It has also been demonstrated[29] that approximately the abundance of Proteobacteria related to Serratia and *E. coli* have increased by three folds. Additionally, it should also be noted that within the intestinal microbiota of Dutch infants who responded with high RVV immune responses, an increase of Proteobacteria, mainly Gammaproteobacteria, such as bacteria related to Serratia, and *E. coli* had occurred[29]. Gram-negative bacteria which were mentioned earlier have the ability to stimulate innate immune responses, including expression of flagella or toxigenic LPS. This means that their cell envelope components could potentially act as natural immune adjuvants for the Pakistani infant population. Through these studies[27,29], we can gain insights into correlations between microbiome composition and RVV immunogenicity. The result from these studies could also be used to understand ways to improve vaccine immunogenicity[27,29].

According to Hill et al[30], supplementing individuals with probiotics can help improve vaccine immunogenicity through modulation of the human microbiota[30]. Since probiotics are considered as live microorganisms, this can be beneficial to the host when given at an adequate amount[30]. Several studies[22,32-34] were done to analyze the efficacy of different vaccines when using different probiotic strains.

In Huda et al[26], microbiota's role on the immune responses to parental vaccination has also been explored within populations of Bangladeshi infants. Among Actinobacteria, the most copious genera found was Bifidobacterium[26]. There are some positive correlations between Bifidobacterium and some adaptive immune responses, including CD4+ and CD8+ T-cell proliferative responses to PPD and TT, the delayed-type hypersensitivity to PPD, and specific IgG responses to TT and hepatitis B (HBV) vaccines[26]. On the other hand, lower vaccine responses were associated with a high abundance of Enterobacteriales and Pseudomonadales or enteric pathogens (i.e., can employ complex strategies to infect and colonize its host)[12,26].

Intestinal Dysbiosis-Caused Inefficacy of Vaccines and Mechanisms

Numerous COVID-19 vaccines were developed in order to initiate conventional immune responses to defend against SARS-CoV-2 infections[35]. Nonetheless, the efficacy of these COVID-19 vaccines may reduce due to various risk factors that can interfere with the immune responses[35]. Association between the severity of COVID-19 and gut dysbiosis caused by multiple risk factors have been shown[36]. Additionally to SARS-CoV-2, the gut microbiota has demonstrated its role in immune responses to vaccination against other viruses in both clinical and animal studies[8]. According to animal models, antibiotic-treated mice or germ-free mice (GF) have shown decreased immune responses in numerous respects. An instance of this particular case has been shown in Kim et al[24,37]. Chen et al[36,38] revealed that combination treatment of mice with a mix of antibiotics including vancomycin, neomycin, metronidazole and ampicillin reduced immune responses to respiratory influenza virus infection. This leads to a reduction in immune responses against respiratory influenza virus infection[39]; additionally, in the lung CD8+ T-cells, CD4+ T-cells and virus-specific antibody titers were reduced and viral titers increased[40]. In a lymphocytic choriomeningitis virus (LCMV) mouse model, the antibiotic-treated mice exhibited delayed virus clearance along with decreased in LCMV-specific IgG

and CD8+ T-cell productions[40]. The study[40] also showed that macrophages had also decreased responses to type I and type II IFNs and impaired capacity to limit virus replication. These animal experiments indicate that gut commensal bacteria are necessary for producing effective immune responses to defend against viral infections. Indeed, *Bifidobacterum longum* subsp[36]. Infantis has been correlated with antigen-specific T cell responses in vaccines for tuberculosis, polio virus and tetanus toxin[26]. Furthermore, dysbiosis caused by deficient protein diets also resulted in reduced immune responses to oral attenuated human rotavirus vaccination, such as decreased cell number of antibody secreting cells, CD4+ T cells, CD8+ T cells and Tregs as well as decreased cytokine production[41,42].

In humans, the roles of the gut microbiota in vaccine efficacy have been evidenced by various approaches[8]. Different responses from the same vaccine are elicited in lower middle-income countries (LMICs) and high-income countries (HICs) and the low efficacy in LMICs was accounted for by gut dysbiosis in the populations[8]. Gut dysbiosis in infants with short-term breast-feeding, malnutrition and diarrhea was linked with the lower efficacy of oral polio vaccines[32]. There is also a clear corresponding relation between gut dysbiosis and the effect of pre-vaccination immune system on the vaccine efficacy as well as the effect of immune status before vaccination on the immune responses to vaccination[9]. For instance, within the population of 65 years old elders in comparison to the younger adults, the efficacy of the influenza vaccine was found to be lower[43]. Among the elderly non-responders of respiratory syncytial virus (RSV) vaccine, there was a noticeable baseline immune profiles with increased expression of CD69, CCR7 and CD127, as well as a higher number of (HLA-DR+) $CD8^+$ and $CD4^+$ T cells, which acts as an indication for a chronic inflammatory status of the individual[44]. Pre-vaccination inflammation in correlation with hypo-responsiveness to HepB vaccination have also been observed[45]. The listed associations could be explained by gut dysbiosis-caused chronic inflammation, resulting in an overall decreased of immune response to vaccinations[45].

The mechanisms responsible of gut microbiota role in vaccine efficacy have been accredited to PRRs or pattern recognition receptors of cells with presence of antigen activated through gut bacterial molecules known as peptidoglycan and flagellin[46]. PRRs are found to be greatly abundant in innate immune cells, deriving in a rapid respond to the stimuli once activated by specific gut bacterial molecules (i.e., termed-immune training)[46]. Through the binding of Nod2 (Nucleotide-binding oligomerization domain-containing protein 2) and PRP by peptidoglycans, cAMP production is then increased, promoting DCs to secrete cytokines. With the activation of Nod2 along with synthetic agonists reconstituted cholera toxin-causing responses found in germ-free mice, the paramount role of Nod-2 in effecting gut-microbiota-stimulated immune responses have been greatly inferred[24,37]. It was also observed that Nod2 stimulation using symbiotic/commensal bacterial played a role in producing the optimal CT-mediated antigen-specific oral vaccination efficacy[24]. The mentioned process is mediated through the induction and subsequence increased levels of IL-1β[24,37]. The TLR5 or Toll-like receptor 5 must be activated by flagellin in order for plasmas cell development and antibody production to take place[19,25]. The clustering of IV and XIVa clostridia can also stimulate TGF-Iβ to activate Treg cells (regulatory T cells), which are crucial in maintaining the equilibrium of immune responses[47]. In comparison to this, gut dysbiosis can lead to chronic inflammation and reduced anti-inflammatory mechanisms by altering butyrate; a commensal bacterial metabolites[48]. Butyrate is widely known to activate Treg cells or regulatory T cells, which will stimulate anti-inflammatory effects[49,50]. According to a mouse model, IgA production in the colon facilitated by butyrate through the activation of GPR109a and GPR41, as well as the inhibition of histone deacetylase was observed[51]. In addition, butyrate plays a crucial role in maintaining the main integrity of the gut barrier[51]. This concept is further supported by the observable damaging outcome resulted from decreased butyrate production. Under this condition, the translocation of bacteria and endotoxin into the extra-intestinal and circulation system organs, which facilitates formation of hyperinflammation due to SARS-CoV-2, causing direct tissue damages are perceptible[49,50]. As a result, specific intestinal microbial dysbiosis which can disrupt immunes responses through inflammation and hyperresponsiveness could lead to the disruption of immune responses induced by COVID-19 vaccinations, thus, affecting the efficacy of COVID-19 vaccines[42,52].

Strategies to Enhance the Gut Microbiota for COVID-19 Immunizations

As gut dysbiosis in COVID-19 has impacted the effectiveness and harmful effects of COVID-19 vaccinations, improving the gut microbiota might boost the efficacy of COVID-19 vaccines and lessen their detrimental effects[42]. Indeed, several ongoing clinical trials[53] examine the effects of modulating the gut microbiome on COVID-19 vaccinations. A clinical trial was conducted to investigate the ability of ABBC1, a yeast-based probiotic, to improve the efficacy of a COVID-19 vaccination as measured by both humoral and cellular responses[35,54,55]. ABBC1 contains 1,3/1,6-glucan, inactive *Saccharomyces cerevisiae*, selenium, and zinc as trace elements. Another clinical experiment[55] utilized a mixture, including three Bifidobacteria to boost COVID-19 vaccination effectiveness and decrease side effects in older individuals with type 2 diabetes. A third clinical trial[56] is evaluating the ability of a functional diet containing 5-ALA-phosphate to boost the effectiveness of COVID-19 vaccinations. 5-ALA-phosphate is recognized to support the homeostasis of gut flora.

Lactobacteria and Bifidobacteria may boost immune responses to COVID-19 vaccines[57]. MAMPs produced by these bacteria can activate TLRs to drive innate and adaptive immune responses[57]. In addition, a clinical experiment (NCT04980560) is now examining the microbiome profiles of vaccinated and infected people[58]. There are several ways to increase the variety of the gut microbiota, including the administration of probiotics, prebiotics, synbiotics, nutraceuticals, trace elements, fecal microbiota transplantation (FMT), and food/energy restriction techniques, such as FMD (fasting-mimicking diets)[36]. These methods have been applied to different circumstances with varying degrees of success[36]. FMT has been used well to treat *C. difficile* infections caused by antibiotic-induced dysbiosis in the gut. FMT is the primary method for rebuilding gut microbiota following *C. difficile* disruption[59]. However, it may have serious side effects, such as infectious diseases[52]. Therefore, it may not be appropriate for use as an adjuvant with COVID-19 vaccinations[60]. Many chronic infectious disorders, including inflammatory bowel disease, have been treated using probiotics, prebiotics, and synbiotics[61]. They are safe, with few documented adverse effects. The organisms from which most probiotics are derived include Lactobacteria and Bifidobacteria. Fructose oligosaccharides, galactooligosaccharides, beta-glucans, and resistant starches are typical prebiotics[36]. Some prebiotics may possess natural antiviral properties[62]. By inhibiting Nsp15, for example, epigallocatechin gallate not only improves gut microbiota but also has a powerful antiviral effect[62]. Both probiotics and prebiotics have been shown to boost influenza vaccination effectiveness significantly[62]. These might enhance the effectiveness of the COVID-19 vaccination, as suggested[63]. Synbiotics can be seen as more superior to probiotics or prebiotics since it contains both commensal bacteria and dietary fiber, which can increase butyrate synthesis in the gut[63]. Butyrate promotes the transformation of antigen activated CD8+ T cells into long-lived memory cells[63].

Newer generations of probiotics have a broader bacterial spectrum and may one day incorporate a COVID-19 vaccine complementing formula[60]. Butyrate-producing bacteria, such as *F. prausnitzii* that can produce butyrate directly are being incorporated into experimental probiotic formulations, which has numerous positive effects, such as enhancing the efficacy and safety of COVID-19 vaccines[64]. An interventional clinical trial showed that *F. prausnitzii* enhanced metabolic pathways and tolerated well. Little is known about the other probiotics of the following generation, such as *Bacteroides acidifaciens*, *Bacteroides ovatus*, *Bacillus pumilus*, and *Bacillus megaterium*[65]. In gnotobiotic mice, *B. acidifaciens* induced a rise in IgA, but *B. ovatus* induced an increase in IgM and IgG[65]. It has been used with nine other probiotics to treat *C. difficile* infections[23]. The suppression of pro-inflammatory signaling pathways may also be crucial for the anti-allergic actions of butyrate[23]. As some of the probiotics of the future generation are capable of producing butyrate, they may have potent anti-allergy properties[23]. Incorporating butyrate into COVID-19 vaccine formulations may help minimize vaccination-associated side effects. Prebiotic polysaccharides have been advocated for COVID-19 prevention and therapy[23]. Each polysaccharide form may have stimulatory or suppressive effects on the immune system. The effect of these polysaccharides on the effectiveness of the COVID-19 vaccine might be examined initially in animal models[23].

A synbiotic formulation (i.e., probiotic + prebiotic) might significantly influence the effectiveness of the COVID-19 vaccination and the avoidance of side effects[63]. An optimum formu-

lation might be developed. With the next generation of probiotic, these may be developed from microorganisms that produce butyrate[66]. Some prebiotics can be given to promote the formation of butyrate, a critical gut microbiota-mediated immune response booster[48,67].

CONCLUSIONS

New COVID-19 cases have decreased significantly now that COVID-19 vaccinations have been widely delivered in affluent nations. Nonetheless, vaccination effectiveness may need improvement, particularly in frail, elderly, and particularly susceptible and chronically ill individuals. Multiple studies have shown that the effectiveness of the COVID-19 vaccination is significantly diminished in individuals with advanced age or chronic illnesses. Although most side effects are mild, those that cause severe problems and fatalities constitute a significant unsolved concern. There may be a connection between gut dysbiosis and the efficacy and harmful effects of COVID-19 vaccinations. Intestinal dysbiosis might be a pivotal contributor to the inefficacy and harmful effects of COVID-19 vaccinations in vulnerable people and the elderly. Indeed, the Norwegian study examining mortality in older, weak patients after immunization increases the possibility of a dysbiotic gut being involved. The improvement of gut microbiota in at-risk groups can promote vaccination efficacy and decrease severe side effects. Modifying the gut microbiota using Bifidobacteria and bacterial metabolites, such as butyrate, might be a realistic strategy as an adjuvant for improving the effectiveness of the COVID-19 vaccination in the elderly who are weak. Next-generation probiotics with or without prebiotics, especially those that cause butyrate-producing bacteria to grow, may be needed to increase the number and variety of gut microbiota, which are essential adjuvant mediators for the COVID-19 vaccine to work and to get rid of any side effects.

Conflict of Interest

The authors declare no conflict of interest.

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Informed Consent

In this research there's no human participation. Thus, informed consent is not needed.

Authors' Contributions

Soothiosoth D. contributed to knowledge of probiotic, data analysis related probiotics as well as molecular immune responses. Pradubyat N. contributed to knowledge of COVID-19 vaccine efficacy and safety as well as molecular immune mechanisms.

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