Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

How does geographical diversity shape vaccine efficacy?

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Vaccination is a cornerstone of public health, saving millions of lives each year by preventing a variety of infectious diseases. Yet, despite global vaccination efforts, emerging research highlights significant geographical disparities in vaccine efficacy and immunogenicity. These variations underscore the critical interplay between immunological factors and environmental, genetic, and nutritional elements across different populations. Our review article aimed to explore the multifactorial reasons behind geographical variations in vaccine efficacy. Also, this study has shown how important host factors like age, obesity, gender, and genetic diversity, especially within the major histocompatibility complex, are in determining how well a vaccine works. Nutritional status, namely deficiencies in micronutrients such as vitamins and zinc, and lifestyle factors including stress, sleep, alcohol consumption, and physical activity are also shown to have profound effects on vaccine-induced immunity. Importantly, our paper also brought to light the influence of microbial and ecological factors, such as the gut microbiome and environmental pollutants, on the immune system's response to vaccination. The findings emphasize the importance of tailoring vaccination strategies to accommodate the unique immunological landscapes shaped by geographical and societal factors. This tailored approach could enhance vaccine efficacy, reduce disparities in vaccine response, and ultimately contribute to the global fight against infectious diseases.

Keywords: Geography, Medical, Immunity, Immunologic factors, Vaccines

Introduction

Vaccines characterize one of the most significant achievements of contemporary medicine. Worldwide vaccination efforts effectively prevent around 2–3 million deaths each year and significantly reduce the occurrence of infectious diseases [1]. Vaccines have effectively eliminated or significantly reduced the prevalence of diseases like smallpox and polio. They also mitigate the severity of diseases in cases of infection and have the potential to prevent the occurrence of specific cancers, such as cervical cancer, by targeting the infectious agent responsible (human papilloma virus). Vaccination additionally diminishes the utilization of antibiotics, thereby mitigating the development of antibiotic resistance [2]. Global coverage with three doses of *Haemophilus influenzae* type b (Hib) vaccine is estimated at 76%, varying significantly between regions, with the World Health Organization (WHO) European Region having 83% coverage and the WHO Western Pacific Region only having 23% [3]. Additionally, international estimates of coverage with the third dose of DTP (diphtheria, tetanus, and per-

tussis) and a polio vaccine decreased from 86% in 2019 to 83% in 2020 [4]. However, recent studies indicate that immunizations may not provide equal protection to all populations. For instance, although over 13 billion doses of coronavirus disease 2019 (COVID-19) vaccines were administered globally, the Eastern Mediterranean region showed the highest COVID-19 vaccine coverage per 100 population [5]. Surprisingly, it has been assessed that vaccine coverage was significantly lower than predicted for 13 out of 16 antigens in 2020 and all assessed antigens in 2021, without specifying which vaccines had the highest coverage rates [6].

Factually, an effective vaccine can prevent disease in two ways: direct protection for high-risk individuals and indirect protection for others to reduce transmission [7]. Despite numerous advances in vaccine technology, there are still concerns and questions surrounding vaccine efficacy and durability [8]. In most cases, a vaccine's efficiency—its capacity to lower infection rates in real-world settings as opposed to regulated clinical trials—is lower than its initial efficacy rate [9]. Most vaccines, like the measles vaccine, have a high level of efficacy, resulting in a reduction of infection rates by almost 98%. Nevertheless, the immune response to hepatitis B weakens with time following frequent immunization [10]. Besides, the decline in antitoxic immunity for diphtheria and tetanus was also noted in an 8-year follow-up investigation [11]. The variability in the vaccination response has significant consequences for the vaccine's protective impact and the duration of immunity it confers [12]. Accordingly, vaccine efficacy is determined by various factors, including vaccine factors (type of vaccine, dose, adjuvant, and administration route), the infectious agent's characteristics (genetic variability), and host factors (age, gender, genetics, nutritional status, gut microbiota, obesity, and immune history) [13]. Therefore, immune responses to vaccines may be influenced by geographic location due to factors such as genetic diversity, environmental exposure, and pre-existing immunity.

Geographical variation in vaccine response has been documented in several studies. Namely, attenuated malaria vaccines that provide nearly 100% protection in high-income countries may only achieve 20%–50% protection in low-income regions. This trend is observed not only for malaria vaccines but also for other vaccines like Bacillus Calmette-Guérin (BCG), rotavirus, and yellow fever vaccines [14]. The immune response to pneumococcal conjugate vaccine (PCV) has been shown to vary by region, with studies conducted in the Western Pacific Region demonstrating a higher geometric mean concentrations (GMC) of antibodies compared to studies in Europe [15]. In addition, the exploration of transcriptional responses to adjuvanted vaccines among populations with varying levels of pathogen exposure and cell-mediated immunological memory demonstrated that geographical variation can indeed affect vaccine responses [16]. Interestingly, while geographic variation is evident, it is also important to note that this variation is not solely attributed to location. Other factors such as genetic diversity, including the human leukocyte antigen (HLA) system on chromosome 6, contribute to individual and population differences in immunological responses to vaccines [17]. Additionally, the composition of the gut microbiome, which can vary by geography and socioeconomic factors, has been identified as a factor influencing vaccine efficacy [18]. Consequently, gaining insight into the impact of these factors on vaccine efficacy presents a chance to improve the overall effectiveness and efficiency of vaccines. In the current article, we reviewed and evaluated the potential impact of geographical-related factors on immune responses to vaccinations. Understanding these factors is crucial for improving vaccination outcomes in regions where standard immunization approaches may be less successful, reducing disparities, and identifying of vulnerable populations, and enhancing public health policies on a global scale.

Immunogenicity of Vaccines

Vaccines require a strong immune response to function properly. Individuals who receive the same vaccination frequently exhibit varying degrees of immunological response, and some may even exhibit unfavorable vaccine side effects [19]. The paradigm of vaccination involves developing antibodies and cytotoxic T cells to create a long-lasting immunization against one or more antigens unique to a pathogen or cancer cell [20]. The capacity of the vaccination to elicit such responses is referred to as "immunogenicity." Modern vaccines function by deceiving our immune system into generating "immunologic memory" against a particular infectious pathogen. The immunologic memory is established through the action of B and T cells and is characterized by the presence of antibodies at adequate levels to counteract the pathogen (Fig. 1). Additionally, there is a prompt generation of effector cells upon encountering the pathogen in real-life situations, which is known as a "recall response" [21]. Immunologic memory has the ability to endure for several decades,

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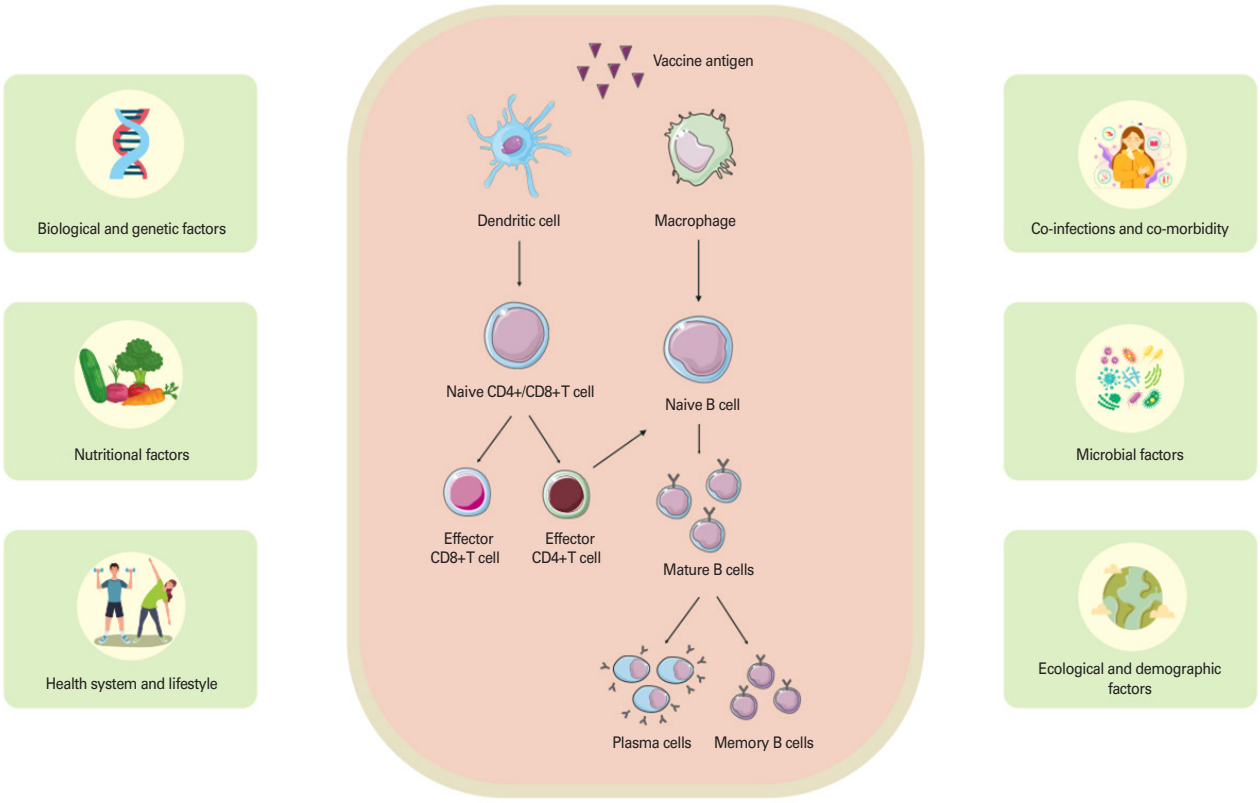

Fig. 1. Schematic representation of the immune response to vaccine antigens and the influencing factors. The central flowchart illustrates the processing of vaccine antigens by dendritic cells and macrophages, leading to the activation of T cells and B cells. The surrounding boxes highlight the various factors that influence this process. The interplay between these factors and the immune response provides a comprehensive view of the complexity of vaccine-induced immunity.

thereby offering an enduring safeguard against infection throughout one's lifetime [22,23]. In order to establish a strong immunologic memory following vaccination, a precise sequence of events must take place. This includes the activation of naive cells, the formation of memory cells, and the maintenance of long-term memory cell stability. Modifying these occurrences, whether in terms of quality or quantity, can substantially impact the efficacy of immune defense induced by vaccines [21].

Nevertheless, the factors contributing to the variability of immune responses to vaccination remain inadequately comprehended, both in terms of inter-individual and inter-population differences. Furthermore, populations particularly vulnerable to infectious diseases, such as infants, the elderly, and individuals residing in low-income and middle-income countries, often experience an immune response generated by vaccines that falls short of the desired level [24]. As an illustration, the levels of antibodies produced by the inactivated seasonal influenza vaccine can differ by approximately 100 times among different individuals [25]. Similarly, the antibody responses to conjugated Hib vaccines and pneumococcal vaccines can vary by up to 40 times. Additionally, the cytokine recall responses can vary by up to 10 logarithmic units in infants vaccinated with BCG [13]. There have been reports of certain vaccines having low immunogenicity and a restricted ability to produce effects on mucosal and cell-mediated immunity (CMI). Numerous factors can influence an immune system's response to vaccinations [26]. The antibody responses to vaccination are affected by various internal factors, including heredity, sex, and age, as well as external factors including, nutrition, stress, and infectious diseases [27]. Understanding factors that may affect interindividual vaccination response variability is crucial to vaccine efficacy.

Biological and Genetic Factors

Age

Age is a critical determinant of vaccine response, particularly in newborns and elderly individuals. Infants exhibit diminished cell-mediated immune responses and lack a fully de-

veloped immune system. Vaccine responses in early life are marked by antibody responses to capsular polysaccharide antigens that are not elicited in the first 2 years of life because the spleen is not fully developed yet, there are not many B cells, and immunoglobulin G (IgG) responses are low [28]. Both the prenatal or gestational age and the postnatal age at which immunization occurs significantly impact the development of antibody responses in early life [29]. A study in Bulgaria investigated the age-related dynamics of post-vaccine humoral immunity to diphtheria and tetanus toxoids. The highest rates of protection against both tetanus toxoid (94.3%) and diphtheria toxoid (79.2%) were observed in the youngest age group (0–4 years). The rate of insufficient protection against both antigens was higher among children with frequent infections [30].

Aging can lead to a decrease in immune competence, which is referred to as immunosenescence [31]. Immunosenescence refers to the decline in the functioning of neutrophils, antigen presenting cells, T cells, and B cells, which leads to an increased vulnerability to infections and reduced effectiveness of vaccinations [21,32]. The majority of vaccines advised for older people contain antigens for which the immune system has already developed an immunological memory (e.g., seasonal influenza virus, Tdap, shingles vaccine) [33-35]. An randomized controlled trial (RCT) study has shown that the young individuals experienced a considerably larger rise in the number of circulating memory B cells following influenza vaccination compared to the older subjects [36]. Multiple studies have demonstrated a delayed and diminished immune response in older individuals who receive vaccines in comparison to the youngest individuals who receive vaccines [37,38]. BNT162b2 vaccination induces adaptive immunity, including antibodies and T cells, but elderly individuals show delayed and less robust responses compared to younger adults [39]. Therefore, researchers must develop or improve vaccines intended for the elderly population to counteract their diminished immune responsiveness. In order to enhance the effectiveness of vaccines for the elderly, numerous approaches have been suggested or executed. These include augmenting the dose of antigen, incorporating innovative adjuvants, employing recombinant or conjugate vaccines, and co-administering multiple vaccines.

Obesity

Another host component related to the vaccination response is the quantity of adipose tissue. Adipose tissue plays a crucial role in regulating the inflammatory state [12]. In comparison to healthy-weight individuals, obese individuals are more susceptible to viral, bacterial, and fungal infections, and they respond poorly to vaccination [40]. The immunity of overweight people may be reduced because the vaccine is mostly distributed in fat, not muscle. It may inhibit absorption and allow denaturation of the vaccine antigen by enzymes. Impaired proliferation and function of antibody-secreting plasma cells is another possibility [41].

According to a study on people who received the trivalent influenza vaccine (TIV), a rise in body mass index (BMI) was associated with a gradual decline in the protective immune response over time. IgG antibodies and hemagglutination-inhibiting (HAI) titers were initially higher in people with a high BMI; however, 12 months after vaccination, the reduction in antibody titers was greater in obese participants than in non-obese participants [42]. Another study revealed that BMI had a distinct correlation with insufficient antibody levels 2 years after receiving the rabies vaccine [43]. Recent COVID-19 vaccine trials have indicated that there is no disparity in vaccine effectiveness between individuals who are normal and obese [44,45]. A preliminary study, however, has shown a correlation between BMI categories and levels of antibodies. The findings of this study indicate a correlation between BMI classes and antibody titers, with more efficient humoral responses observed in under- and normal-weight individuals [45]. As well, according to a recent study, among Italian healthcare workers, a higher BMI is linked to a lower antibody response to the COVID-19 vaccine [45]. Overall, obesity and BMI exert a substantial influence on the immune response to vaccination. Furthermore, immunometabolic dysregulation poses a significant challenge to the development and execution of effective vaccines for obese individuals.

Gender

Gender and sex are significant determinants in comprehending immunization, encompassing aspects such as the frequency and severity of adverse reactions, vaccine delivery, and efficacy. Gender variations in immunization outcomes have been observed across age groups for vaccine-preventable diseases, with women generally reporting more systemic and local adverse reactions and higher antibody responses than men, although this is not always the case [46]. These variations have been noted in reactions to vaccinations that employ various technologies, such as the Calmette-Guerin vaccine and vaccinations against influenza, mumps, yellow

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fever, rubella, and measles [47]. Various biological factors have been suggested to be involved, such as disparities in the immune system, hormones, genetics, and microbiome between males and females [47,48]. Case in point, women were more likely to experience adverse events like injection site pain, myalgias, and headaches after receiving the inactivated TIV than men were. Additionally, women exhibited a stronger immunogenic response to TIV, with even half a dose of the vaccine eliciting humoral responses comparable to those seen in men who received the full dose [49].

Vaccinating against yellow fever is another example. This vaccine can cause local inflammation, fever, discomfort, headaches, and exhaustion. In women, macrophages and dendritic cells secrete more inflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1b, IL-6, and CXCL10 (C-X-C motif chemokine ligand 10), which may cause these adverse reactions to occur more often [47]. Although there are notable biological and behavioral distinctions between males and females, research indicates that there are no substantial gender disparities in the effectiveness of the COVID-19 vaccines, particularly among younger age groups [50,51]. But the risks of adverse effects were higher in females of all ages, according to a study including four cross-sectional investigations. This was especially true after the second dose of the COVID-19 mRNA vaccinations [52]. Therefore, in order to mitigate negative responses in females, it is imperative to take into account the disparities between sexes when developing the COVID-19 vaccine [51].

Different vaccination reactions occur in men and women and in people with varying degrees of stress due to a process called neuroendocrine-immune interaction. Progesterone, estradiol, and testosterone are sex hormones that influence the functional capabilities of immune cells. The impacts of these sexual hormones vary depending on the dosage. This is particularly pertinent for estrogen and progesterone, as their levels fluctuate throughout various phases of the menstrual cycle, during pregnancy, and following menopause [47]. Stress hormones, such as cortisol and adrenaline, can decrease the generation of antibodies and the activation of T cells in response to vaccination, especially if the stress is chronic or occurs prior to or during vaccination.

During pregnancy, sex hormones like estradiol, estriol, progesterone, and prolactin undergo substantial changes in levels. Additionally, it is characterized by a phase of immunological inactivity. Findings from an observational study highlight the importance of sex hormones in the response to the pertussis vaccine during pregnancy. The study that looked at the immune response to a pertussis vaccine during pregnancy and the role of sex hormones discovered that anti-pertussis toxin IgG antibody levels were much higher in women who were not pregnant than in women who were pregnant. This may be because of the higher levels of hormones during pregnancy [53]. Furthermore, the menopause exerts a discernible influence on the female immune system. Postmenopausal women experience a decline in immune function due to reduced amounts of estrogen, which is a main concern [54]. Hormone replacement therapy in women demonstrated advantageous effects on the immune system, as it partially reversed immunological changes associated with menopause [55]. A study examines the effects of menopause and estrogen therapy on the frequency of lymphocyte subsets and the immune response to the seasonal influenza vaccine. The findings indicate that post-menopausal women who undergo estrogen therapy experience improved maintenance of naive B cells, reduced production of inflammatory cytokines, and decreased levels of IL-6 [56]. Another investigation reveals that testosterone and estrogen's opposing effects on genetic regulation may cause male hepatitis B vaccine nonresponse. Estrogen makes monocytes release IL-10, while testosterone destroys IgG and immunoglobulin M (IgM). This may partially explain gender vaccination response variability [41]. Hence, the consideration of neuroendocrine-immune interaction is crucial in the development and implementation of effective vaccines for diverse populations.

Many countries encourage immunization during pregnancy to save infants from tetanus, pertussis, and influenza. At birth, infants whose mothers are immunized against dTpa (diphtheria, tetanus, and acellular pertussis) exhibit greater concentrations of antibodies to these antigens in comparison to infants whose mothers are not given the vaccine [57-60]. Although pregnant vaccination has the potential to augment the infant's response to particular vaccines [61]. Research has demonstrated that elevated levels of maternal antibodies can impede the humoral immune response of infants following vaccinations. The blunting effect, also known as the diminished humoral response, has been shown for a number of vaccines, including those against measles, mumps, tetanus, pertussis, and influenza [62-64]. A RCT found that Tdap vaccination during pregnancy leads to higher levels of antibodies in infants but lower levels after the primary vaccine series [65]. As a result, blunting may be a worry for the development

and use of future vaccines.

Additionally, neonatal immunity is affected by maternal infections during pregnancy. This includes being exposed to viruses, bacteria, and parasitic helminths while pregnant, which can change the immune system in specific and general ways, changing the chances of getting perinatal infections and the efficiency of vaccines. Maternal schistosome infection could drive changes in offspring's immune system development, potentially altering vaccination responses and immune disorders [66]. Cohort studies have shown that maternal helminth infection, which affects offspring immune priming and cord blood IL-10 levels, can lower protective IgG levels in response to Hib and diphtheria vaccination [67,68]. On the other hand, a study in Ecuador found that antenatal maternal helminth infections were not associated with reduced antibody responses to infant vaccines but rather with modestly increased immunoglobulin A (IgA) responses to oral vaccines.

Delivery and circadian rhythms

The vaccine delivery pathway is a vital factor in determining the efficacy of vaccination. For the recipient's immune system to properly recognize the antigen, it is necessary for the antigen to be in its original shape and in the ideal quantity. Currently, the predominant method of vaccine administration is through intramuscular or subcutaneous injection. Nevertheless, in recent years, extensive research has been conducted to explore various alternative methods of administering vaccines and identify new areas of the body that can serve as potential sites for vaccine delivery [69].

In a RCT involving Japanese adults aged 65 years and older and administered a quadrivalent, high-dose influenza vaccine, participants who received the vaccine via the intramuscular route exhibited greater geometric mean titers (GMTs) and seroconversion rates than those who received the vaccine via the subcutaneous route [70]. Similary, elderly individuals who were administered the alum-adjuvanted recombinant hepatitis B virus (HBV) vaccine intramuscularly had a significantly higher likelihood of being responders compared to those who were immunized subcutaneously [71]. A phase IV clinical trial compared the safety and immunogenicity of Havrix, an intramuscular hepatitis A vaccine, given subcutaneously in 45 children with haemophilia and intramuscularly to 41 nonhaemophlic siblings. The study concludes that Havrix is safe and immunogenic when administered subcutaneously in children with haemophilia [72]. In contrast, Fessard et al. [73] discovered that the antibody response was greater when the vaccination was administered intramuscularly. Furthermore, a separate study has revealed that there is no substantial disparity in immunogenicity when comparing the subcutaneous and intramuscular administration routes for the HBV vaccine [74].

Furthermore, the temporal variation in the immune system's response to challenge during different times of the day implies that the scheduling of vaccinations might similarly impact antibody responses [75]. A study on the antituberculosis vaccine BCG found that morning vaccination elicited stronger trained immunity and adaptive immune responses compared to evening vaccination [76]. In specific instances, the efficacy of influenza vaccines is enhanced when administered in the morning as opposed to the afternoon [77]. Another study investigates the impact of circadian rhythm on the immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines among healthcare workers. Results show that morning vaccinations stimulate a stronger serological response and long-term protective immunity, crucial for vaccine efficacy and long-term protection [78].

Genetic diversity

Genetic variations in gene encoding virus receptors, antigen presentation, cytokine production, and immune cell activation and differentiation have been shown to affect vaccine efficacy and safety [79,80]. Numerous investigations have been conducted on the impact of genetic polymorphism within the major histocompatibility complex (MHC) region on the diversity of immunological responses. It contains genes essential for both the adaptive and innate immune systems, and it has been divided into three regions (class I, II, and III). The impact of MHC variations on the immune response to the vaccine was first discovered by observing a significant excess of HLA-DR7 and a total absence of HLA-DR1 in individuals who did not show any response to the hepatitis B vaccine [81]. The HLA region has been extensively studied in terms of the immunity induced by HBV vaccines. Vaccination failure has been linked to some particular HLA-class II alleles. Specifically, the genetic variants DRB1*0301, DRB1*0701, and DQB1*0201 have been linked to instances where vaccination fails. Additional antigens, including DRB1*0101, *1301, *1501, and DPB1*0401, seem to enhance the immune response to vaccines [82].

Genetic diversity in loci outside of the HLA area influences the immune response triggered by HBV vaccination [83].

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Polymorphisms in many genes, including IL-1 family members, TNF-α, GNB3 (guanine nucleotide-binding protein), IL-2, IL-4, IL-6, IL-10, IL-12β, and haptoglobin, have been linked to changes in the strength or kinetics of the immune response to the HBV vaccination, specifically in terms of antibody production and lymphocyte proliferation. Genetic variations in interferon-γ (IFN-γ) activity may potentially influence the extent of immune responses induced by HBV vaccination [83]. Besides, regression analysis and mean antibody level comparison showed appreciable differences in IgG and neutralizing antibody levels after genotype stratification of rs1042522 in the *TP53* in the whole cohort and specifically in the mRNA-based vaccine group [84]. The *TP53* gene encodes the p53 tumor suppressor protein, which plays a crucial role in the antitumor immune response and response to immunotherapy [85]. Additionally, other genetic determinants that appeared as significant modifiers of IgG and neutralizing antibody responses to SARS-CoV-2 vaccines include *ABO*, *APOE*, *ACE2*, and *HLA* [84]. The rubella vaccination has also exhibited comparable HLA correlations. The HLA-DQA1*0201 allele has been linked to enhanced antibody responses following measles immunization [86]. A study by Tan et al. [87] found that genetics significantly influences the variation in antibody levels following measles, mumps, and rubella vaccinations. The study involved 100 Caucasian twin pairs aged 2–18 years old who had received at least one vaccine dose. Heritability was 88.5% for measles, 38.8% for mumps, and 45.7% for rubella, indicating that genetics significantly influences antibody responses [87]. Despite the fact that the MHC covers 40% of the hereditary influence on hepatitis B surface antigen (HBsAg) responsiveness, compelling evidence suggests that genes other than HLA class II antigens also have an important effect. The study by Höhler et al. [88] found that MHC class III genes can influence B-cell responsiveness to HBsAg vaccination. Nonresponders had a higher rate of C4A gene deletions and non-expressed C4AQO alleles [88].

The genetic heterogeneity of toll-like receptor (TLR) also has a significant impact on vaccine responses. TLR7 and TLR8 play a crucial role in eliminating viruses by recognizing single-stranded RNA. Certain investigations have demonstrated that hypermorphic TLR8 polymorphisms improve the vaccine-induced response to live attenuated vaccines. A case-control study discovered a significant correlation between a hypermorphic TLR8 polymorphism and BCG-induced protection against *Mycobacterium tuberculosis* infection, linking function to immune protection in response to a live attenuated vaccination in humans [89]. A recent study involving 550 children who received trivalent-inactivated influenza vaccine found that certain single nucleotide polymorphisms in TLR7–1817G/T (rs5741880) and TLR8–129G/C (rs3764879) genes were associated with lower odds of having post-vaccination HAI titers ≥40 [90]. In addition, evidence has shown that TLR7 and TLR8, involved in viral sensing, play a key role in the response to trivalent influenza vaccination in adults within 24 hours of inoculation [91]. Nevertheless, in a study of 12-month-old Australian infants, receptor protein expression was examined to assess the functionality of these polymorphisms. Results showed no functional effects of TLR7 or TLR8 polymorphisms on receptor expression, measles-specific cellular responses, or measles vaccine antibody responses [92].

It has also been established that genetic ancestry is a substantial factor in determining vaccine responses. Several studies have examined the impact of genetic race on the efficacy of the same vaccination response. A study involving 2,872 healthy children, adolescents, and young adults found that genetically defined race significantly influences measles immunity after vaccination. People with African-American ancestry show higher antibody and cell-mediated immune responses compared to those with Caucasian ancestry [93]. The differences in Hib disease incidence and Hib conjugate vaccination efficiency among ethnic groups reveal genetic impacts on the immunological response to Hib vaccine [27]. In this sense, discrepancies in the effectiveness of the Hib vaccine were noted in Alaska and Finland, despite the administration of the identical Hib conjugate vaccine (Hib polysaccharide capsule conjugated with diphtheria toxoid vaccine; polyribosylribitol phosphate [PRP]-D) [94]. In another study, newborns from Chile had 3 times greater levels of post-vaccination PRP antibodies than infants from Belgium [95]. Researchers have extensively studied the effect of genetics on vaccine response, and we have only mentioned a portion of it. Overall, the findings from the studies demonstrate that genetic polymorphisms appear to play an important role in explaining variations in immune responses to vaccines. Understanding the role of genetics in vaccine response may help to improve vaccine design and delivery, as well as personalize vaccine strategies based on each individual's genetic profile.

Nutritional Factors

Nutritional factors are crucial for maintaining the proper

functioning of the immune system and preventing the occurrence of infectious diseases. An optimal immune response necessitates a sufficient nutritional status of the host [96]. Micronutrient insufficiency hampers immunological functioning by impacting the adaptive antibody response and T-cell-mediated immune response, resulting in the disruption of the balanced host response [97]. Studies conducted on humans, especially older individuals, have found a correlation between deficiencies in immunological markers and low levels of micronutrients such as vitamin C, vitamin B6, Fe, and zinc [98,99]. The significance of nutrition in bolstering the immune response extends to ensuring strong reactions to vaccination as well. There has been a link between such immune impairments and poor vaccine outcomes [100]. For instance, a RCT demonstrated that enhancing the consumption of fruits and vegetables has been found to enhance the antibody response to the Pneumovax II vaccine in older individuals, thus establishing a connection between a feasible dietary objective and enhanced immunological function [101]. Additionally, decreased zinc levels are linked to a decline in the ability to respond to diphtheria and influenza vaccination, and a similar decrease in responsiveness to pneumococcal polysaccharide vaccination has been observed in individuals with lower levels of serum vitamin B12 [102-104].

Vitamin A and D play important roles in cell-mediated and humoral antibody responses [97]. Supplementing with vitamin A in several infectious diseases, has demonstrated the capacity to enhance the immune response to certain vaccines, such as those for rabies [105] and measles [106]. Likewise, a RCT investigated the effects of vitamin D supplementation on the response to influenza vaccination in older individuals with vitamin D deficiency. The study found that vitamin D supplementation increased the levels of transforming growth factor-β in the plasma following influenza vaccination without improving the generation of antibodies. It was proposed that supplementation appears to guide the polarization of lymphocytes towards a tolerogenic immunological response [107]. Additionally, there is also a definite link between vitamin D insufficiency in hemodialysis patients and reduced antibody responses to hepatitis B vaccination [108]. Clinical outcomes also demonstrate a function for vitamin E in immunological capability. In a study, people over 65 years who received 60 mg or 200 mg of the vitamin daily showed improved reactions to certain vaccinations when compared to the placebo group [109].

The situation with vitamin C is similar. Vitamin C administration has been linked to enhanced interferon production and has been studied for its potential use in the prevention of vaccine failure. Supplementing with 2 g of oral vitamin C for each of the three injections of the rabies vaccine stimulated increased serum interferon-α (IFN-α) levels 24 hours after the injection, suggesting that "vitamin C is an effective stimulator of interferon production" [110]. Finally, marginal selenium (Se) insufficiency can also impair immunity. A 12-week study on healthy adults found that supplementing with yeast enriched with Se increased T-cell proliferation, IL-8, and IL-10, but also reduced granzyme B content of CD8 cells and unaffected mucosal flu-specific antibody responses after flu vaccination [111]. In a separate investigation, adults with low Se status in the United Kingdom who received 50 μg/day or 100 μg/day of Se supplementation had an enhanced immunological response to a poliovirus vaccine, and fewer mutant viral strains emerged [112]. As a result, ensuring nutritional adequacy via providing micronutrient supplements, fruit and vegetable consumption, incorporating probiotics and prebiotics, and provide nutritional education and awareness campaigns may help to improve vaccine efficacy and safety.

Health System and Lifestyle

During the last three decades, a sequence of studies has recorded the influence of psychological aspects on the immune system's reaction to vaccines. Substantial research has proven that stress, depression, anxiety disorders, and unhealthy behaviors can hinder the immune system's ability to respond to vaccines. This impact is particularly notable for susceptible populations, such as older adults. Psychological variables play a role in both the frequency and intensity of vaccine-induced side effects [9]. These mental disorders frequently lead to unhealthy behaviors, such as smoking, consuming low-quality food, having inadequate sleep patterns, being physically inactive, and excessively using alcohol.

A prevalent psychological factor that can influence the immune system and vaccination response is stress. Multiple studies have demonstrated that stress can disrupt the formation, sustenance, and efficacy of antibodies against diverse pathogens, including hepatitis B, measles, smallpox, rubella, influenza, and SARS-CoV-2. For instance, a meta-analysis of 13 studies investigated the link between psychological stress and antibody responses to the influenza vaccine. Evidence demonstrated that higher levels of stress were connected with lower levels of antibodies [113]. In another study, medi-

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cal students taking exams had different virus-specific antibody and T-cell responses to a hepatitis B vaccine depending on academic stress and social support [114]. Further, an investigation analyzed the antibody levels in 60 undergraduate students following administration of the meningitis C conjugate vaccine, demonstrating that psychological stress has the potential to diminish the immune system's reaction [115].

In another series of studies, it has been demonstrated that certain occupations are more prone to stress. Caregiving, particularly for individuals with dementia requiring 24-hour care, is a chronic stressor that can reduce social interactions, limit participation in hobbies and increase the risk of anxiety and depression. An investigation demonstrated that chronic stress can reduce IgG antibody response to pneumococcal bacterial pneumonia immunization among dementia caregivers. Compared to controls, caregiver antibody titers were lower after 3 months and 6 months of vaccination [116]. Poorer antibody responses to vaccinations are seen in even younger caretakers. A study evaluated antibody responses to vaccination in parents of disabled children with usually developing children. Researchers found that caregivers had a lower antibody response to the B/Malaysia immunization than controls. Caregiving has a negative influence on both older and younger parents of children with developmental difficulties [117]. Overall, several types of vaccines can be negatively affected by both chronic stressors (such as caregiving) and acute stressors (such as an academic examination), leading to a compromised immune response, notably in terms of antibody production. Two more studies examined the vaccination response in the presence of psychological stress. A cohort of 83 participants was investigated and monitored before, during, and after vaccination in order to determine whether moderate stress could affect the antibody response to influenza vaccination in healthy young adults. Results showed that higher stress levels led to poorer antibody responses [118]. Another study of 59 men discovered that stress might cause psychological and physiological changes. IL-6 levels increased with typhoid vaccinations, causing depression and high blood pressure [119]. Additionally, stress can heighten the risk of vaccine-related adverse effects, including fever, pain, and inflammation. For example, following the administration of the influenza virus vaccine, chronic depression was found to be linked with heightened and prolonged inflammatory reactions [120].

Like stress, depression affects various aspects of the immune system's response to vaccines. Before receiving vaccination, depressed individuals frequently show dysregulated immune systems, characterized by elevated levels of inflammation [121]. The chronic inflammation could potentially disrupt the immune response to the vaccine [122]. Unmedicated depressed people with prior varicella zoster exposure had fewer cell-mediated responses to a vaccine than depressed people taking antidepressants and non-depressed individuals, indicating they may be at risk for a recurrence [123]. Patients undergoing hemodialysis who experienced a higher degree of depressed symptoms exhibited a diminished antibody reaction to the hepatitis B vaccine [124]. Moreover, exacerbating the situation, depression symptoms might intensify and extend the immediate inflammatory reaction to a vaccination [125].

Loneliness and a small social network also have the potential to hinder the functioning of the immune system and can even cause changes in how vaccines work in healthy and young individuals. A study of 83 undergraduate students found that individuals with high levels of loneliness and restricted social networks had a lower antibody response to the influenza vaccination component. People who encountered both causes had the lowest antibody response [126]. In another study, researchers found a link between stressful life events such as bereavement, social support, marital status, and contentment, and influenza vaccination antibody responses in an older community. Bereavement decreased influenza strain responsiveness, while marital contentment and marriage increased peak responses [127]. These data show that social network size is more important for younger adults than marital loss, which may be more immunologically significant for older adults.

Given the link between the COVID-19 pandemic and increasing symptoms of psychological disorders (i.e., psychological stress) and the vaccination efforts occurring around the world, it is especially crucial to investigate the efficacy of vaccines in individuals with mental disorders [128]. In this sense, a 676-person study found that lower social cohesion and loneliness were linked to lower COVID-19 vaccination antibody responses. This suggests that social cohesion, or feeling "in it together," is essential for the vaccination response, emphasizing its importance during the pandemic [129]. Each of the aforementioned mental disorders has the potential to lead to unhealthy behaviors, which can have a negative impact on the immune system's functioning and the body's response to vaccination. Therefore, improving healthy behavior and lifestyle could help optimize vaccine efficacy

and safety, and to prevent vaccine failure or complications.

Unhealthy behaviour

In humans, short sleep habits (<6 hours per night) are linked to shorter lifespans, a higher viral infection risk, and lower antibody titers following vaccination. It has been shown that shorter sleep duration was associated with a lower secondary antibody response and a decreased likelihood of being clinically protected from hepatitis B at the conclusion of the vaccination series [130]. As well, short-term sleep deprivation before vaccination seems to have a detrimental effect on antibody levels following influenza vaccination, hence reducing the effectiveness of the influenza vaccine [131]. The influence of sleep quality before the vaccination on immunological responses has been studied. COVID-19 pandemic research in South Korea indicated that frequent bedtime electronic device use decreased sleep quality and increased COVID-19-related adverse outcomes [132]. Additionally, sleep following vaccination can increase the number of T-helper 1 (Th1) cytokine-producing cells and double the frequency of antigen-specific T cells [133].

The influence of alcohol intake on human health is intricate and regulated by various elements, including drinking patterns and quantity, genetics, the specific organ system under investigation, as well as the gender and age of the individual. Although there is evidence that moderate alcohol use improves the response to traditional vaccinations [134], more evidence suggests that excessive amounts of alcohol consumption can alter the immune response. Among individuals diagnosed with hepatitis B, HBV indicators are common in drinkers. Alcohol, because of its capacity to induce cirrhosis, has been implicated as an autonomous risk factor for impaired immune response. However, some research has found no correlation between alcohol use and hepatitis B vaccination. More studies demonstrate that both young individuals who consume alcohol and those who regularly consume alcohol are more likely to experience difficulties following immunization with the Oxford/AstraZeneca vaccine (AstraZeneca, Cambridge, UK), which may lead to a decrease in the efficiency of COVID-19 vaccines [135].

Smoking has an impact on the immune system and its ability to respond. Several vaccine humoral responses and maintenance immunity have been studied in conjunction with the impacts of cigarette smoking on the immune system. Some research has linked active smoking to reduced vaccine-induced antibodies and suggests that the connection between tobacco smoking and reduced vaccination effectiveness may also be influenced by inflammation [136]. Smoking and male gender were associated with a reduced response to the hepatitis B vaccination. Smoking has the potential to impact cellular and humoral-mediated immune responses in people who smoke. Nicotine inhibits the antibody-forming cell response and intracellular calcium response by interfering with the antigen-mediated pathway in T cells [41]. A research of 200 healthy Slovak people aged 24–65 years assessed the immunogenicity of a booster dosage and the long-term durability of humoral diphtheria immunity. In smokers, seroconversion rates and GMCs of diphtheria antibodies were decreased, suggesting antibody depletion [137]. Furthermore, active smoking raised the likelihood of low-avidity human papillomavirus (HPV)16/18 IgG antibodies in 16% of vaccinated women [138]. Additionally, some real-world investigations have shown a possible relationship between smoking and the humoral response to COVID-19 vaccinations. Smoking and the humoral response to the BNT162b2 mRNA COVID-19 vaccination in Italian healthcare professionals were examined. After two dosages, participants were tested for SARS-CoV-2 spike-receptor-binding domain-specific IgG antibodies. Even after adjusting for sex, age, and previous infection, smokers and non-smokers had significantly different vaccine-induced IgG titers [139]. Another study assessed anti-SARS-CoV-2 spike IgG antibody titers after the BNT162b2 immunization and tobacco and moderate consumption of alcohol. The findings reveal that heated tobacco products and moderate alcohol use may reduce the COVID-19 vaccination immunological response [140].

Exericise

Multiple studies conducted on elderly and young individuals in good health provide evidence that acute physical activity can improve both antibody and cell-mediated reactions to vaccination antigens [141]. An investigation examined the impact of exercise on the response to pneumococcal vaccinations in 133 young, healthy adults. Results showed that exercise groups showed a greater increase in antibody levels and larger responses than control groups. This suggests exercise's effectiveness as a vaccine adjuvant, especially in weaker responses [141].

Furthermore, regular, vigorous exercise improved the influenza vaccination immunological response in a 62-year-old people. Anti-influenza IgG and IgM were higher in active participants, while peripheral blood mononuclear cell prolif-

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eration was lowest in sedentary people [142]. Also, a RCT involving 112 healthy older adults in two urban US communities found that exercising significantly increased varicella zoster virus-specific CMI levels [143]. A study found that 90 minutes of light-to-moderate-intensity exercise post-immunization can increase serum antibody response to three different vaccines: 2009 pandemic influenza H1N1, seasonal influenza, and COVID-19. The study found that exercise consistently increased antibody to each vaccine 4 weeks post-immunization, with IFN-α potentially contributing to the benefit. All of this suggests that regular physical activity raises antibody levels after vaccination by a large amount, particularly in older adults. Mainly because physical exercise releases pro- and anti-inflammatory cytokines, which prevent inflammation and boost immune cells like neutrophils, natural killer cells, and macrophages [144].

Co-infection and Co-morbidity

Co-infections

Mixed infections can result in an increased susceptibility to one or both infectious agents, suppression of one or both, or an increased susceptibility to one and suppression of the other [145]. Concomitant infections also appear likely to impact the effectiveness of vaccinations. Vaccinating kids suffering from malaria against tetanus, typhoid, or bacterial meningococci poses a challenge [146]. Cytokines and other immune-mediated molecules can directly or indirectly influence parasites. In a similar way, helminth infections that stimulate defensive T helper type 2 immune responses can also suppress Th1 responses, potentially leading to the aggravation of simultaneous infections or an inability to mount an effective immune response to vaccination in infections that are regulated by Th1 responses. An investigation examined the consequences of helminth infection on the effectiveness of malaria vaccinations. The study indicates that helminth infections may also impact the development of a robust Th1 immune response to an expected malaria vaccine. Therefore, the implementation of broad anti-helminth control programs could enhance the effectiveness of malaria vaccines in stimulating the desired immune responses [147]. Evidence indicates that the presence of helminths may have a greater detrimental impact on live vaccinations [148]. The results of a study have demonstrated that the efficacy of BCG vaccination as a live vaccine in combating *M. tuberculosis* is diminished in people who are consistently exposed to chronic helminth infections [149].

Furthermore, it has been established that long-term *schistosome* or *Onchocerca volvulus* infection might alter the immunological response to the tetanus or BCG vaccine, leading to reduced anti-vaccine reactions [150]. Additionally, prenatal exposure to helminth antigens may be associated with a shift towards a type II response profile following BCG vaccination at birth, emphasizing the potential importance of early life exposures [151]. A separate study conducted in Uganda discovered that infection with *Schistosoma. mansoni* in children results in a diminished antibody response to catch-up measles immunization. It is suggested that implementing effective control measures for schistosomiasis could potentially enhance vaccine efficacy [152]. Studies on direct helminth exposure and hepatitis B responses indicated that previous infections can greatly decrease vaccination responses [153]. Multiple studies indicate that human immunodeficiency virus (HIV)-infected patients, particularly those with CD4+ T cell counts <500/μL, exhibit diminished reactions to the hepatitis A vaccine [154,155]. Nonetheless, some research has shown that those who have contracted helminth or malaria have improved immune responses against tetanus, HPV, and polio. This implies that, depending on the vaccination type and the individual, the effects of these different illnesses on immune responses may vary [156,157].

Co-morbidities

Comorbidity is a prevalent condition that affects the immunological response to vaccination, as it impairs both the innate and adaptive immunity of persons with chronic diseases. These alterations make persons with comorbidities more vulnerable to infectious diseases and less willing to respond to vaccinations. Here, we investigate immunological responses to vaccines in the context of various common comorbidities. Additional data is gathered and shown in Table 1 [158-206]. Infections are common in people with chronic liver disease (CLD), particularly those with cirrhosis. As liver disease advances, the efficacy of the majority of immunizations diminishes. Therefore, these patients demonstrate weak humoral and cellular immune reactions to the vaccines. Vaccination against hepatitis B is recommended for all patients with CLD, regardless of whether or not they have cirrhosis. Although these vaccinations are highly immunogenic in healthy people (>90%), seroconversion is low in those with CLD, and vaccine efficacy decreases as the severity of the liver disease increases [207]. In addition, individuals with liver

Table 1. Vaccine immunogenicity in participants who had at least one co-morbidity compared to healthy controls

Co-morbidity	Disease	Vaccine target	Vaccine platform	Vaccine immunogenicity comparison	Reference
Chronic liver disease	Cirrhosis	Influenza	Inactivated	Similar	[159]
	Cirrhosis	Influenza	Inactivated	Similar	[160]
	Cirrhosis	Influenza	Inactivated	Similar	[161]
	Cirrhosis	SARS-CoV-2	Inactivated	Lower	[162]
	Cirrhosis	SARS-CoV-2	mRNA	Lower	[163]
	Cirrhosis	SARS-CoV-2	mRNA	Lower	[164]
	Cirrhosis	Hepatitis B	Recombinant	Lower	[165]
	Cirrhosis	Hepatitis B	Recombinant	Lower	[166]
	CHB	SARS-CoV-2	Inactivated	Similar	[167]
	CHB	SARS-CoV-2	Inactivated	Similar	[168]
	CHB	Influenza	Inactivated	Similar	[161]
	CHC	Hepatitis B	Recombinant	Lower	[169]
	CHC	Hepatitis B	Recombinant	Lower	[170]
	LTR	Influenza	Inactivated	Similar	[171]
	LTR	Influenza	Inactivated	Lower	[160]
	LTR	SARS-CoV-2	mRNA	Lower	[172]
	LTR	SARS-CoV-2	mRNA	Lower	[173]
	LTR	Hepatitis B	Recombinant	Lower	[174]
CVD	CVD	SARS-CoV-2	mRNA	Lower	[175]
	CTP	SARS-CoV-2	mRNA	Lower	[176]
	AIIRD	SARS-CoV-2	mRNA	Lower	[177]
	Hypertension	SARS-CoV-2	mRNA	Lower	[178]
	Hypertension	SARS-CoV-2	Inactivated	Lower	[179]
Diabetes	T2D	Influenza	Inactivated	Similar	[158]
	T2D	Influenza	Inactivated	Similar	[180]
	T2D	SARS-CoV2	mRNA	Lower	[181]
	T2D	SARS-CoV2	Inactivated	Lower	[182]
	T2D	SARS-CoV2	Inactivated	Lower	[183]
	T2D	SARS-CoV2	Inactivated	Lower	[184]
	T2D	Hepatitis B	Inactivated	Lower	[185]
	T2D	Hepatitis B	Inactivated	Lower	[186]
	T1D	Hepatitis B	Recombinant	Lower	[187]
	T1D	Hepatitis B	Recombinant	Lower	[186]
	T1D	Hepatitis B	Recombinant	Lower	[188]
	T1D	Hepatitis A	Recombinant	Lower	[189]
	T1D	SARS-CoV-2	mRNA	Similar	[190]
	T1D	SARS-CoV-2	mRNA	Similar	[191]
	T1D	Influenza	Inactivated	Lower	[192]
	T1D	Influenza	Inactivated	Lower	[193]
Cancer	HM	SARS-CoV-2	mRNA	Lower	[194]
	CLL	SARS-CoV-2	mRNA	Lower	[195]
	HM	SARS-CoV-2	mRNA	Lower	[196]
	ST	SARS-CoV-2	mRNA	Lower	[197]
	ST	SARS-CoV-2	mRNA	Lower	[198]
	ST	SARS-CoV-2	Inactivated	Lower	[199]
	HM	SARS-CoV-2	Inactivated	Lower	[200]
	HM	Infuenza	Inactivated	Similar	[201]
	HM	Infuenza	Inactivated	Similar	[202]
	HM	Infuenza	Inactivated	Lower	[207]
	CLL	Infuenza	Inactivated	Lower	[204]
	MBL	Infuenza	Inactivated	Lower	[204]
	HM	Infuenza	Inactivated	Lower	[205]
	HM	Hepatitis B	Recombinant	Lower	[206]

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mRNA, messenger RNA; CHB, chronic hepatitis B; CHC, chronic hepatitis C; LTR, liver transplant recipients; CVD, cardiovascular disease; CTP, cardiothoracic transplant patients; AIIRD, autoimmune inflammatory rheumatic diseases; T2D, type 2 diabetes; T1D, type 1 diabetes; HM, hematologic malignancies; CLL, chronic lymphocytic leukemia; ST, solid tumors; MBL, monoclonal B cell lymphocytosis.

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cirrhosis experience reduced rates of seroprotection following the completion of the HBV vaccination series [208]. In a study, patients with liver cirrhosis who received two doses of the mRNA-based vaccination BNT162b2 according to the normal procedure produced antibodies against SARS-CoV-2, but their median IgG titer was much lower than the control group. The control group had steady antibody titers, but liver cirrhosis patients had quick and severe decreases [209]. A comparative study examining the immune response of individuals with cirrhosis and liver transplant recipients to SARS-CoV-2 revealed that 63% of liver transplant recipients experienced seroconversion following the second vaccination. In contrast, cirrhotic patients exhibited lower levels of anti-SARS-CoV-2 antibodies [210].

Additionally, multiple studies have demonstrated that influenza vaccinations significantly decrease mortality, hospitalization, and occurrences of acute coronary syndromes among individuals with coronary heart disease and heart failure (HF). A study with 29 people with HF and 17 people who were healthy showed that the cytotoxic T lymphocyte responses to the flu shot were adequate in the HF patients but not higher than in the healthy controls. However, patients with HF exhibited a diminished antibody-mediated response to H3N2 [211]. Morever, hypertension has emerged as a prominent risk factor for the development of cardiovascular diseases. Multiple studies have established a correlation between hypertension and decreased antibody titer. Furthermore, hypertension has been linked to both vaccine misresponses and a malfunctioning immune system [212]. Despite this, a recent study examined the antibody titer in a group of 248 healthcare workers 7 days following the second dose of the BNT162b2 vaccine. The results indicated that hypertension did not appear to be linked to any variation in vaccine-induced immune responses [213].

Besides, diabetic patients have a significantly higher susceptibility to infections as a result of their impaired immune system. Hospitalizations and mortality due to vaccine-preventable diseases are more common in people with diabetes, whether type 1 or type 2. Immunization is the best defense against diseases that can be prevented through vaccination. Consistent with this, previous research has demonstrated that individuals with diabetes mellitus (DM) may have a weakened antibody response to certain vaccines, such as those for influenza and hepatitis B. However, with recent advancements in vaccine production, people with DM are now capable of generating an acceptable immune response following immunization. Type 2 DM (T2DM) is a common chronic inflammatory condition among older individuals. In older populations, particularly in patients with diabetes, influenza vaccination has demonstrated limited effectiveness. Nevertheless, a study revealed no disparity in antibody responses between elderly individuals with diabetes and those without any health conditions [158].

Another investigation compared the long-term immunogenicity and safety of an influenza vaccine in type 2 diabetics and nondiabetics. The elderly diabetic group had a lower seroprotection rate, but their long-term immunogenicity profiles were similar. Consequentially, regardless of diabetes, age, and prevaccination, titers are predicting long-term immunogenicity [214]. A prospective study assessed the safety and immunogenicity of the recombinant hepatitis B vaccine in subjects with and without DM. The study found that the vaccine is immunogenic in diabetes patients and has a similar safety profile to healthy controls [215]. Several investigations examine diabetes-related COVID-19 vaccine efficacy and safety. Diabetics have a strong immune response to COVID-19 immunization, but it is weaker than in non-diabetics. Poor glycemic control suppresses antibody production, while optimal control performs like healthy controls [216]. A study evaluated the response to the SARS-CoV-2 vaccine in subjects with diabetes and controls. Both type 1 DM and T2DM are associated with a reduced early response to vaccination. However, after a period of 6 months, individuals, both with and without diabetes, experienced a notable decline in antibody levels, with no discernible distinctions observed between the two groups [217].

Moreover, cancer patients are more likely to contract COVID-19, influenza, and hepatitis B, and vaccinations for these infections are suggested. However, individuals with cancer have an adequate response to vaccines, but it is lower, and greater doses, booster doses, or novel adjuvants may be required to improve vaccine efficacy. An extensive study conducted in France revealed that the rates of influenza vaccination among different groups of patients with weakened immune systems, such as those who have undergone transplants or have malignancies, varied between 59% and 72% [218]. A research investigation carried out in the Netherlands during the influenza season revealed that breast cancer patients exhibited sufficient antibody responses to the influenza virus vaccine [219]. According to a prospective study performed at Roswell Park Cancer Institute, influenza vaccination induces an adequate immune response in patients with

colorectal cancer [220].

Recent reports indicate that individuals with cancer experience a decrease in antibody titers after receiving the mRNA COVID-19 vaccination. However, boosting at 21 days significantly increased efficacy in solid cancer patients [221]. Another COVID-19 vaccine study in cancer patients demonstrates a single dose produces weaker and heterogeneous serological responses in hematological and solid malignancies. But a second dose increases SARS-CoV-2 spike protein seropositivity in all cancer cohorts [222]. A systematic review examined cancer patients' COVID vaccine safety and efficacy. After a second dose, solid tumor patients had 88% seroconversion and hematologic malignancies at 70% [223]. Overall, vaccination in cancer patients is safe, tolerable, and effective, but the type of malignancy, anti-cancer therapy, and patient demographics can affect it.

Additionally, several studies assessed the immunogenicity of the influenza vaccination in persons with sickle cell disease (SCD). A study assessed the seroprotective post-vaccine H1N1 antibody response in children with SCD. Most subjects were able to mount an influenza-specific antibody response against the inactivated H1N1 vaccine [224]. Researchers compare influenza vaccination coverage and morbidity between Medicaid members with and without sickle cell illness. Results suggest SCD enrollees have higher influenza vaccination coverage than non-SCD enrollees [225]. Healthy and asthmatic, sickle cell, systemic lupus erythematosus (SLE), and solid organ transplantation (SOT) children were tested for influenza A and TIV vaccination immunological responses. Seroprotective hemagglutination inhibition (HI) titers increased significantly in high-risk groups. Asthma and SCD children exhibited the highest seroprotection following TIV, while SOT and SLE children had lower rates [226]. On the other hand, a study conducted on people with sickle cell illness revealed compromised immune responses to a trivalently inactivated vaccine, indicating that the long-term consequences of SCD, such as splenic atrophy, can impact the body's ability to respond to vaccination [227]. This finding demonstrates the significant function of the spleen in initiating the production of antibodies. Beta-thalassemia major patients in Iran were tested for influenza vaccination antibodies. patients were divided into three groups: single dose, double dose, and control. The double dose group showed higher GMT, seroconversion rate, and antibody titer [228]. Many thalassemia major patients need splenectomies, which increases post-splenectomy infections. Immunizing asplenic patients against influenza could decrease their death risk by 54% [229]. Prior research has demonstrated that specific vaccines elicit suboptimal immune responses in individuals who are infected with HIV, commonly referred to as people living with HIV. However, the results of SARS-CoV-2 vaccine responses have demonstrated that it elicits strong immune responses that are similar to those observed in healthy individuals [230].

Microbial Factors

The human microbiome, especially the digestive tract, has garnered interest for its role in biological processes. The microbiota helps with nutrition acquisition, vitamin generation, and intestinal development and has been linked to resistance to diseases like inflammatory bowel disease, obesity, and ectopic diseases. The microbiota may also influence the metabolism of certain drugs and toxins, potentially affecting the body's processing of oral vaccines [231]. Additionally, it can function as an immunomodulator and play a role in our organism's response to other vaccinations [232]. Several studies have consistently shown that an increased presence of the *Actinobacteria phylum* is linked to enhanced vaccine responses, while a higher prevalence of *Bacteroides* is associated with reduced responses [233-235].

The variations in the effectiveness of oral vaccinations against cholera, rotavirus, and poliovirus in different geographical regions can be attributed to disparities in gut flora [236]. A study in Ghana found that intestinal microbiome composition significantly correlates with rotavirus vaccine (RVV) efficacy. The study compared the microbiomes of 6-week-old infants, who were matched to Dutch infants, and found that the gut microbiome of RVV responders was more similar to Dutch infants [237]. A different inquiry, examines the interaction between humans and fecal bacterial communities and the impact of live oral vaccination on Ty21a (typhoid fever vaccine). Results show that individuals with a multiphasic immune response to vaccination have a richer and more diverse microbiota community, suggesting vaccine immunogenicity and efficacy may be linked to this structure [238]. In addition, certain research has shown that microbiome can enhance both humoral and cellular responses to vaccines. The study conducted by Hagan et al. [239] in 2019 discovered a notable reduction in IgG1 and IgA responses among adults with low initial levels of H1N1-specific antibodies after a 5-day course of broad-spectrum antibiotics. A

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research of 249 Bangladeshi children discovered that the quantity of intestine *Bifidobacteria* strongly affected CD4+ T-cell and immune responses to several parenteral vaccinations at 2 years of age, implying that intestinal microbial ecology could influence human immunological memory cells [24]. Beside that, there is evidence to suggest that microbiome-derived epitopes have the potential to mimic the antigenic determinant of a particular vaccine. This, in turn, could boost the vaccine's ability to provoke an immune response [240]. These findings suggest an indirect connection between gut microbiota and the effectiveness of vaccines [239].

In addition, probiotics are beneficial commensal microbes that exist in fermented foods and are typically eaten by the host. They reduce infections by influencing the innate and adaptive immune systems [241]. Research indicates that various strains of probiotics demonstrate additional effectiveness when used in conjunction with specific types of vaccines. It has been documented that *Lacticaseibacillus rhamnosus GG* and *Bifidobacterium animalis* can influence immune responses in humans [242,243]. Both probiotics and prebiotics have been shown in clinical trials to have protective effects against influenza infection. In addition, there have been studies focused on the usefulness of adjuvant supplementation of probiotics or prebiotics with measles vaccination. Supplementing influenza vaccines with probiotics or prebiotics prior to vaccination enhanced the immune response to particular strains of influenza viruses, such as H1N1, H3N2, and B strains [244]. Another study suggests that combining prebiotics and probiotics with influenza vaccination can significantly improve HI antibody titers, potentially resulting in a 13.6%–20% increase in immune responses [245]. The study found that responses to seasonal influenza vaccination were numerically greater in the probiotic group than the placebo group [246]. Subsequent research discovered probiotics boost antibody responses to oral polio, salmonella, rotavirus, and *Vibrio cholera* vaccinations, according to other research.

In addition, probiotics enhanced immunological reactions in children who received oral vaccinations for Hib, tetanus, diphtheria, and HBV [231]. The probiotic action of *Lactobacillus plantarum* was examined in other investigations. The findings demonstrated a significant increase in the level of fecal secretory IgA in newborns who received the probiotic [247]. Probiotic supplementation may be a safe and natural way to increase the effectiveness of vaccinations, particularly in susceptible groups like the elderly. Administering *L. coryniformis* to the elderly population, in relation to the COVID-19 vaccine, boosted the immune response in individuals who had a prior infection with the SAR-CoV-2 virus. Additionally, it showed potential for improving the immune response in older individuals who had not been infected with the virus [248]. Therefore, adjuvant administration of probiotic formulations can promote intestinal commensal participation in innate and CMI, thereby assisting in vaccine responses to infectious diseases while preserving immunological tolerance [249].

Ecological Conditions

Vaccination response varies depending on the host and environmental circumstances. Adhering to a healthy lifestyle and limiting detrimental environmental exposures may serve as an important public health approach in conjunction with the development of efficacious pharmaceuticals and vaccines [250]. In addition to the obvious effects of large-scale natural disasters, pollution and climate change have exerted a major but less apparent influence on human health [251]. Children are more susceptible to environmental exposure compared to adults [252]. In general, there is evidence to suggest that pollution may contribute to the onset of autoimmune disorders via chronic inflammation, a process that can subsequently compromise the effectiveness of vaccinations [253].

Chemical substances, including pesticides, herbicides, and solvents, have the ability to disturb the immune system by interfering with the endocrine system, modifying the microbiota, and impacting the epigenome. phthalic acid esters (PAEs) are commonly used in chemical synthesis and do not form covalent bonds with products. PAE exposure affects the immunological response. In this sense, a study conducted in Taiwan discovered that exposure to PAEs during early childhood had an impact on the vaccine immunological response of children, leading to a reduction in hepatitis B antibody levels [252]. A further study demonstrated that higher levels of perfluorinated compounds in 5- and 7-year-old children from the Faroe Islands were linked to a weakened immune response to standard childhood vaccinations [254]. Likewise, it has been demonstrated that heavy metals can result in reduced levels of vaccination antibody titers in children residing in regions where electronic debris is dismantled [255]. Heavy metals, such as mercury, lead, and arsenic, can also disrupt the immune system by affecting immune cell function and survival, modifying immune gene expression, and producing oxidative stress and inflammation. A study con-

ducted in Guiyu, China, explored how chronic exposure to heavy metals and metalloids affects children aged 3 to 7 years. The exposed group exhibited greater heavy metals and metalloids and fewer vaccination antibodies [256].

Exposure to sunlight inhibits the delayed-type hypersensitivity response among individuals to different bacterial and fungal antigens [257], suggesting that irradiation can reduce immunologic memory and cellular and humoral immune responses. In addition, ultraviolet radiation (UVR) can inhibit immune function by causing apoptosis, reducing cytokine production, and disrupting the DNA of immune cells. Studies evaluating the association between solar UVR and vaccination in different nations found that winter vaccinations produced stronger antibody responses than summer ones against influenza [258]. Furthermore, a separate study investigated the immune response of children aged 4–5 years to the rubella vaccine. Results showed a strong correlation between the immune response and the season of vaccination. The winter-inoculated group had significantly higher GMTs and a higher percentage of infants properly immunized [259]. UVR can suppress immunity through skin chromophores and T and B regulatory cells, potentially reducing the efficacy of vaccination [260].

Integrating considerations of local environmental and genetic factors into public health initiatives for vaccination campaigns is crucial for maximizing the effectiveness and safety of these campaigns. Conducting local epidemiological studies can help identify the specific genetic factors that contribute to the spread of diseases in a particular area. This information can be used to tailor vaccination strategies to the local context [261]. For instance, throughout the COVID-19 pandemic, investigating mutations in samples from several countries revealed a variety of mutation frequency patterns [262,263]. This can have a direct and indirect impact on drugs and vaccine development methods. Besides, environmental monitoring can help identify factors such as air and water quality, which can impact the spread of diseases. This information can be used to develop targeted vaccination strategies that address these environmental factors [264]. On the other hand, advanced technologies such as genomics and precision medicine can help identify genetic variations that may affect an individual's susceptibility to certain diseases or their response to vaccines. These technologies can also help identify environmental factors that may impact the spread of diseases [265]. In fact, an interdisciplinary approach that involves experts from various fields such as epidemiology, genetics, environmental science, and healthcare can help ensure that vaccination campaigns are comprehensive and effective [266]. Moreover, there is evidence that some factors, including distance from the equator, accounted for a lot of the heterogeneity in the impacts of BCG among trials. In the case of BCG vaccination, more than 10 randomized trials in the United States, India, Canada, the United Kingdom, and South Africa, between latitudes 10° and 50°, showed the vaccine was more protective against tuberculosis with increasing distance from the equator [267]. Hence, vaccination response may be adversely affected by environmental factors, including heavy metals, UVR, and chemical compounds; vaccination design and administration may therefore necessitate special attention to these concerns.

Demographic Disrtibutions

Vaccine coverage is increasing worldwide, even in low- and middle-income nations. A complex combination of demographic, structural, social, and behavioral factors can affect vaccination coverage. The determinants of coverage that are not related to socio-demographic factors can be categorized into five dimensions (the 5As): Access, Affordability, Awareness, Activation, and Acceptance. Research has shown that access to vaccinations can be influenced by factors such as place of birth [268], geographical location of vaccination sites [269], regular interaction with the healthcare system [270], and the ease of accessing vaccines [271]. These factors are closely linked to the rate at which people choose to receive vaccinations. According to a study that looked at US children between the ages of 19 and 35 months, state vaccine financing policies had a significant impact on heptavalent PCV7 uptake rates [272]. Further, many parents today may lack awareness of the dangers posed by vaccine-preventable diseases, such as tetanus, measles, pertussis, or poliomyelitis. This lack of awareness stems from not having personally witnessed the devastating effects of these diseases. Consequently, some parents do not deem vaccination against these diseases to be of sufficient importance [273]. An enhanced understanding of vaccines enhances their acceptance and adoption. Attitudes towards influenza vaccination among healthcare workers in the United Kingdom were the focus of one study. Results showed people's willingness to get vaccinated increased when given more information about the risks and benefits [274]. Activation involves the strategies employed to encourage individuals who have the intention of

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receiving a vaccine to actually get vaccinated. To enhance the adoption of influenza vaccination among children, it is recommended to broaden the scope of promotion efforts and intensify engagement with healthcare providers. Children who attended healthcare facilities equipped with reminder systems were 5 times more likely to receive a flu vaccine compared to those attending facilities without such systems [275].

However, the immunogenicity and effectiveness of many vaccines differ substantially by population and geography. Specifically, there have been reports of poorer responses in low-income compared to high-income and rural versus urban areas [276]. The majority of under-5 deaths worldwide are attributable to infectious diseases in developing countries, which are home to two-thirds of the global population. Immunization programes must succeed in protecting the health of people in developed and developing nations and preventing disease spread during international travel and globalization [277]. Oral vaccinations, regardless of whether they are composed of living or non-living viral or bacterial components, provoke reduced immune responses or exhibit lesser effectiveness in developing nations compared to affluent nations [278]. For instance, Rotarix protects infants in Europe from severe rotavirus-associated gastroenteritis by more than 95% after 1 year, but its effectiveness in Malawi is less than 50% [279,280]. Serum responses to oral cholera vaccines were also evaluated in three pediatric vaccine trials that were conducted in Sweden and Nicaragua. The reactions of the children from Nicaragua were less dramatic than those of the children from Sweden [281].

In the case of parenterally administered vaccines, empirical data indicates that vaccines exhibit reduced efficacy in low- and middle-income nations compared to high-income nations. In sub-Saharan Africa, the efficacy of the measles vaccine is below 75%. The reason for the reduced efficacy of vaccines in low- and middle-income countries is uncertain; however, malnutrition might be a contributing factor [282]. According to a study that compared the effectiveness of the BCG vaccine in Malawi and the United Kingdom, the United Kingdom had a greater increase in IFN-γ responses compared to Malawi [283]. A separate study has shown that the levels of neutralizing antibodies against the yellow fever vaccine are lower and decline more rapidly in Uganda compared to Switzerland [148].

A number of vaccines have lower efficacy or immune responses in rural areas and tropical low-income countries than in urban areas. The immune modulation by parasitic infections like helminths, common in rural tropical areas, may suppress vaccine responses. A study in Ugandan found lower vaccine efficacy and immune responses in rural and tropical low-income countries. The researchers measured plasma antibody and whole blood assay cytokine responses to tetanus toxoid and purified *M. tuberculosis* protein derivatives. Rural areas had lower concentrations of PPD-specific IFN-γ, IL-13, and TT-specific IgG, but higher concentrations of PPD-specific immunoglobulin E [284]. Similarly, studies have demonstrated that the immune responses to influenza and tetanus vaccines are diminished in rural areas of Gabon when compared to urban areas [156,285].

Nevertheless, there are still millions of individuals globally who have not received the vaccine. In developed countries, particularly the United States and European countries, a significant number of individuals who have not received vaccinations can be attributed to the increasing reluctance of parents to vaccinate their children, which is influenced by the anti-vaccination movement. According to Gust et al. [286], only 33% of parents who were surveyed identified as "immunization advocates" and were actively seeking vaccinations for their children. The evidence suggests that in developed nations, people have faith in the usefulness and significance of vaccines but doubt their safety [287]. Vaccine hesitancy continues to impede the achievement of complete population immunization against highly contagious diseases. Based on data from WHO/United Nations International Children's Emergency Fund, the three primary factors cited for vaccine hesitancy were: (1) concerns regarding the balance between risks and benefits; (2) insufficient knowledge and awareness regarding vaccination and its importance; and (3) factors such as religion, culture, gender, and socioeconomic status influencing attitudes towards vaccination [288]. This means social and health factors affect the massive vaccination, and attitude-based population segmentation can help develop targeted behavior-change communication campaigns. An Indian study examined urban and rural attitudes toward COVID-19 vaccines in Tamil Nadu. The study included 564 unvaccinated people. Over 50% had positive attitudes towards the vaccines. Older individuals with higher education were more likely to trust vaccines, while younger, women, rural residents, and low-income laborers were highly mistrustful [289]. Hence, it is imperative to consider the unique circumstances of a specific region when formulating strategies to promote the adoption of vaccination programs.

Conclusion

The current article highlights the critical need for a tailored approach to vaccination strategies that account for multifaceted factors influencing vaccine efficacy, which can vary significantly across different populations and geographical regions. Additionally, the article brings to light the significance of ongoing research and the development of vaccines that can adapt to these diverse factors to ensure broad and lasting protection across all populations. Given the complexity of the factors influencing vaccine response, further studies are essential to deepen our understanding of how these elements interact and to identify new strategies to overcome the challenges they present. Through continued research, collaboration, and innovation, we can strive towards a future where everyone, regardless of where they live or their background, can benefit from the life-saving protection that vaccines offer.

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