


## REVIEW

# Host factors and vaccine efficacy: Implications for COVID-19 vaccines

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**Abstract**

The efficacy of the vaccines varies between individuals and populations. The immunogenicity of the vaccine is influenced by various factors, including host factors. Previous studies have shown that host factors affect the effectiveness of vaccines, which may be true about COVID-19 vaccines. In this review, we evaluate the possible association of host factors with vaccine efficacy with a special focus on COVID-19 vaccines.

**KEYWORDS**

COVID-19 vaccine, COVID-19, host factors, SARS-CoV-2, vaccine efficacy, vaccine immunogenicity

## 1 | INTRODUCTION

Vaccines are the most important measure for the control of infectious diseases. An effective vaccine can protect people with two mechanisms: direct protection, high-risk people are vaccinated to prevent the disease, and indirect protection, where other people are vaccinated to reduce transmission.<sup>1</sup> Despite many advances in vaccinology, there are concerns and questions about the efficacy and durability of vaccines.<sup>2</sup>

The history of vaccination dates back to 1798 when Edward Jenner developed the smallpox vaccine, which was the first viral disease to be eradicated by the vaccine. In the following years, more vaccines were produced and many improvements were made.<sup>3</sup> Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was observed in late December 2019 with an outbreak of respiratory infections and its genomic sequence was published in early January.<sup>4,5</sup> Since then, efforts have begun to design different vaccine platforms around the world. After a short time, a number of vaccines were licensed for emergency use. However, efforts are being made to increase the effectiveness of the vaccine, especially in the case of new strains of the virus.<sup>3</sup>

Vaccine efficacy varies between individuals.<sup>6</sup> Antibody responses to yellow fever and hepatitis B vaccine differ between individuals by more than 10 and 100 times, respectively. These variations in the vaccination response have implications for protective effect and the duration of immunity provided by the vaccine. Worryingly, some

infections occurred in vaccinated people. This means that in some people the vaccine is not effective (nonresponders). Actually, vaccine efficacy is influenced by the characteristics of the infectious agent (genetic variation), vaccine factors (type of vaccine, adjuvant, dose, and administration route and schedule), and the host factors (age, sex, genetics, nutritional status, gut microbiota, obesity, and immune history).<sup>6,7</sup> Here, we evaluate the possible effect of host factors on the efficacy of COVID-19 vaccines mostly based on previous studies on previous vaccines. Understanding the effect of these factors on vaccine efficacy provides an opportunity to enhance the efficacy and effectiveness of vaccines.

## 2 | THE EFFECT OF AGE ON VACCINE RESPONSE

Age is one of the most important factors influencing vaccine response, especially in infants and aged people. Infants have weak cell-mediated immune responses and do not have a mature immune system.<sup>6</sup> They produce lower levels of antibodies.<sup>8</sup> On the contrary, maternal antibodies can interfere with the vaccination response of neonates. Although maternal immunization during pregnancy protects the infant in the first months of life, it can also have possible side effects: it is hypothesized that maternal antibodies attach to vaccine epitopes in infants and prevent the presentation of vaccine epitopes to B cells and activation of B cells, thereby reducing

antibody production.<sup>9</sup> For these reasons, neonates may have a weak response to the vaccine. Given that COVID-19 infection is severe in the elderly, not infants and children, here, we discuss the effect of age on vaccine response in the elderly.

The risk of serious outcomes associated with COVID-19 disease increases with age, and elderly adults account for the majority of COVID-19-related hospitalizations and deaths in word wild. On the contrary, COVID-19 infection is mostly asymptomatic or mild in children.<sup>10</sup>

With aging, the immune system decreases. The elderly have a weaker immune response and are known to have lower responses to many vaccines (including seasonal flu vaccines) than middle-aged people.<sup>11</sup> Changes in the immune system in the elderly lead to immunosenescence, which is accompanied by a significant reduction in the strength of the immune system.<sup>10</sup> Immunosenescence can lead to lower rates of immune responses to the vaccine in elderly adults.<sup>12</sup> Inflammation increases with age, this phenomenon is called inflammaging.<sup>10,12</sup> Inflammaging is an age-related change in the immune system, defined by low-grade inflammation. One study suggested that inflammaging is identified by high levels of C-reactive protein and was related to reduced antibody responses to the COVID-19 vaccine.<sup>13</sup>

Another host factor associated with vaccine response is the amount of adipose tissue. The adipose tissue plays an important role in adjusting the inflammatory state. Adipose tissue has a major role in regulating the inflammatory status, in lean and insulin-sensitive states, adiponectin acts as an anti-inflammatory force in adipose tissue and regulates the production of anti-inflammatory cytokines and the polarization of macrophages toward the M2 anti-inflammatory phenotype. Leptin, on the contrary, is produced in a state with high adipose tissue and induces inflammation by stimulating the production of inflammatory cytokines. With age, the amount of adipose tissue increases and acts as an auxiliary factor in causing inflammation and inflammaging.<sup>14</sup>

The composition of the gut microbiota changes with age, in addition, there is a "leaky gut" in the elderly. As intestinal permeability increases in the elderly, microbiota enter the bloodstream from the intestine, causing low-grade inflammation and contributing to inflammaging.<sup>12</sup>

As well as, due to thymus degeneration in old age, the generation of naive T and T-cell receptor repertoires diminishes, which may weaken the immune response.<sup>10</sup>

Nutritional status is another factor associated with vaccine response in the elderly. Adequate nutritional status of the host is necessary to establish an effective immune response.<sup>15,16</sup> Dietary deficiencies and malnutrition are frequent among the elderly.<sup>11</sup> Therefore, it may affect immune responses in the elderly.

In line with the evidence, a group of researchers recommends providing nutritional supplements for all persons over 70 years for several weeks before vaccination to increase immunity generated by COVID-19 vaccines.<sup>11</sup>

Compared with other age groups, adults have a higher prevalence of underlying diseases.<sup>10</sup> Comorbidities have been shown to

be a risk factor for the development of severe infections, such as kidney disorders, with impaired kidney function, the level of immune response is also affected and decreased.<sup>17</sup> As well as, comorbidities act as a contributing factor to induce leaky gut.<sup>12</sup>

It has also been suggested that frailty, an aging syndrome affects the antibody response generated by vaccines in elderly people.<sup>18</sup>

A recent study reported heterogeneity of age-dependent immune response to the SARS-CoV-2 BNT162b2 vaccine after the first dose. Antibody levels were lower in the elderly compared to younger people after the first dose of the vaccine, especially in those over 80 years of age.<sup>19</sup> In another study, neutralizing titers were higher in the young age group compared to the old age group, 22 days after the first dose of SARS-CoV-2 BNT162b1 messenger RNA vaccine.<sup>20</sup>

Also, an animal study showed evidence of lower immunogenicity in aged mice than in younger mice after a single dose of the ChAdOx1 nCoV-19 vaccine.<sup>21</sup>

Therefore, vaccination of the elderly is a priority and it is very important to optimize the effectiveness of the vaccine in this population. One way to optimize the efficacy of vaccines for aged people is to use high doses.<sup>22</sup> A meta-analysis study found that high doses of influenza vaccine in the elderly were more immunogenic than standard doses.<sup>23</sup>

In general, immunosenescence, inflammaging, poor diet, diversity and gut microbiota composition, high drug intake (especially antibiotic as a major factor for microbiota disruption), and high prevalence of comorbidities are related to lower vaccine responses in aged people.

### 3 | THE ROLE OF SEX DIFFERENCES IN VACCINE RESPONSE

Sex is the biological difference between males and females. Male sex is a risk factor for the severity of COVID-19 infection and mortality.<sup>24</sup> On the contrary, previous research show that sex also affects vaccine responses. Studies on influenza and hepatitis vaccines appear to indicate that, compared to men, women have a higher immune response after being vaccinated with these vaccines.<sup>25,26</sup>

Immune responses vary between two sexes, which may lead to sex disparities in vaccine responses. Women have more hemagglutination inhibition antibody titers than men after the influenza vaccine.<sup>25</sup>

While sex differences affect immune responses, antibody production, vaccine responses, and treatment, then gender should be considered as a variable in these studies.<sup>27</sup>

Inactivated H1N1 vaccine was injected into male and female mice, which induces immunity mainly through antibodies. After vaccination, female mice had higher antibody responses. Compared with antibodies from male mice, antibodies from vaccinated females are more effective in protecting naïve males and females during the challenge with the H1N1 drift variant virus, and this protection is related to higher specificity and affinity of antibodies for the H1N1 virus in female mice.<sup>28</sup> As well as showed that part of the difference in vaccine response between the

sexes may be due to epigenetic factors. Females showed increased expression of toll-like receptor 7 (Tlr7) due to an epigenetic mechanism in female B cells. Tlr7 expression was higher in B cells of vaccinated women than men and was related to lower DNA methylation in the Tlr7 promoter region in females.<sup>28</sup>

However, studies on sex differences in the efficacy of COVID-19 vaccines need to be designed, data from a meta-analysis of COVID-19 vaccines showed greater efficacy in men than women in vaccinated individuals, in this study, men had a reduced risk for a new infection than women, after vaccination, men were 33% less likely to develop COVID-19 than women.<sup>29</sup>

In addition to immune system differences between the sexes, sex-based disparities in antibody response may be related to the effect of sex hormones and immune regulatory genes on chromosome X, genes such as Tlr7 are located on the sex chromosomes,<sup>18,24</sup> and high testosterone levels repress vaccine response in men; however, it is controversial.<sup>18</sup> In short, the role of the sex variable in the vaccine response should be explored in clinical trials.

#### 4 | THE ROLE OF NUTRITIONAL STATUS IN VACCINE EFFICACY

Effective immune responses are formed in the host with proper nutritional status.<sup>16</sup> Evidence suggests that vaccines are often less effective in low- and middle-income countries than in high-income countries. For example, in sub-Saharan Africa, the measles vaccine is less than 75% effective. It is not clear why vaccines are less effective in low- and middle-income countries, but malnutrition can contribute.<sup>30</sup> Vitamins and minerals are needed to create effective immune responses. Micronutrient deficiencies may lead to impaired immune responses, resulting in weak vaccine response,<sup>11</sup> for example, evidence suggests that iron deficiency is associated with lower vaccine efficacy.<sup>31</sup>

Iron deficiency is very common in the world. There is evidence that iron deficiency may lead to poor vaccine responses.<sup>31</sup> Iron deficiency and anemia at the time of vaccination of children in Kenya have been reported as prognostic factors for weak response to some vaccines including diphtheria, pneumococcal, and pertussis. In addition, the use of iron supplements at the time of measles vaccination strengthened the vaccine immunogenicity.<sup>30</sup>

The link between iron status and the immune system is not fully understood. However, iron deficiency appears to have a negative effect on the adaptive immune system and leads to poor vaccine response.<sup>31</sup> Iron is required for lymphocyte development, and homozygous mutations in Transferrin receptor protein 1 cause immunodeficiency and a decrease in memory B-cell count in children.<sup>30,32</sup>

Several mechanisms have been proposed for the effect of iron deficiency on the adaptive immune system: Iron deficiency reduces T lymphocytes proliferation and activation. It also has a negative effect on the number of B cells and their function.<sup>30</sup>

The possible effect of vitamin D on vaccine immunogenicity has been investigated.<sup>33,34</sup> The existence of vitamin D receptors on immune

cells, as well as the multiple roles of vitamin D in the immune system, suggest a potential effect of vitamin D on the immune system.<sup>34</sup> Vitamin D induces the synthesis of antimicrobial peptides (strengthening the innate system) and reduces severe inflammatory responses. It has a protective role against infections by affecting the immune system, boosting innate immunity, and modulating excess inflammation.<sup>35</sup> The association of vitamin D with vaccine immunogenicity is still under study. Animal studies on the diphtheria vaccine have shown that the active form of vitamin D induces dendritic cells maturation at the vaccine site and their migration to lymph nodes, where these cells activate T and B lymphocytes and trigger strong antibody responses.<sup>36</sup>

Studies on the effect of vitamin D on vaccine response have conflicting results and further studies are needed.<sup>33,34</sup> One study suggests that vitamin D deficiency at the time of vaccination is related to a weaker immunogenic response to hepatitis B vaccination.<sup>34</sup> In contrast, a group of researchers reported that low levels of vitamin D in individuals were associated with higher antibody titers after papilloma vaccination.<sup>37</sup> According to the contradictory results in this regard, further studies are needed to clarify this relationship. In short, nutritional interventions (use of probiotics and nutritional supplements) may be an easy and appropriate strategy to increase the immunogenicity of vaccines.

#### 5 | OBESITY OR BODY MASS INDEX (BMI) AND VACCINE RESPONSE

Obesity is associated with increased susceptibility to infectious diseases.<sup>38</sup> Obesity can lead to chronic inflammation and dysregulation of immune responses, including disorders in cytokine production, decreased function of natural killer cells, changes in the balance of CD8<sup>+</sup> T/CD4<sup>+</sup> cells, and reduced response to viral vaccines.<sup>39,40</sup>

Obesity is accompanied by weak responses to the hepatitis B vaccine. The results showed that people with a BMI greater than 25 have a lower response to hepatitis B vaccination than individuals with a BMI less than 25.<sup>39</sup> In another study, however, this result was not observed.<sup>38</sup>

Humoral responses after the COVID-19 vaccine are less effective in obese people than in nonobese people.<sup>41</sup> Finally, obesity is a risk factor for the severity of COVID-19 infection, and obesity as a variable that affects vaccine efficacy should not be ignored. Interventions such as weight loss recommendations may be needed to improve the effectiveness of the COVID-19 vaccine.

#### 6 | THE ROLE OF GUT MICROBIOTA IN VACCINE RESPONSE

The human gut microbiota is made up of symbiotic microbes that act as an obstacle and have many activities in the digestive tract. It is mainly composed of obligate anaerobes, up to 100 times more numerous than aerobic and anaerobic bacteria. The two main bacterial phyla present in the flora are *Bacteroidetes* and *Firmicutes*. The intestinal microbiome is involved in the digestion and absorption of nutrients and produces a number of metabolites in the gut. As well as microbiome produces

antimicrobials and it plays a protective role by preventing pathogens from adhering to the intestinal membrane.<sup>42</sup> As about 70% of immune cells are located in the digestive system, the intestinal flora has a broad regulatory effect on the immune system. In other words, there is the active interplay between gut microbiota and immunity, the innate and adaptive immune response is influenced by the gut microbiota, which has an immunomodulatory effect. The gut microbiota varies greatly between individuals, throughout life, and between different populations around the world.<sup>43–45</sup> Therefore, microbiota can play a role in creating individual differences in the immune response of the vaccine. Differences in vaccine immunogenicity between high-income and low-income countries may be due to differences in diet-affected microbiota composition.<sup>43</sup>

How microbiota affects the vaccination response is still under study, although the association between individual microbiota composition and vaccination response has been reported. The high prevalence of Firmicutes is related to strong cellular and humoral responses to oral vaccines.<sup>12,44</sup> Increased abundance of Proteobacteria is associated with a weaker immune response.<sup>12,45</sup>

The ability to manipulate the microbiota (including nutritional interventions, probiotics, and rational use of antibiotics as a major factor that destroys the microbiota) to modulate the immune response holds great promise in improving vaccination effectiveness.

## 7 | THE EFFECT OF HOST GENETIC POLYMORPHISMS ON VACCINE RESPONSE

Host genetics is one of the factors that influence vaccine outcome. Studies have suggested that genetics can be applied to foresee the effectiveness of vaccines and design more effective and personalized vaccination strategies.<sup>18</sup>

There is evidence for an association between HLA polymorphisms and vaccine response. One study reported that HLA-DPB1\*02:02, DPB1\*03:01, and DPB1\*14:01 were associated with increased antibody responses to the HBV vaccine.<sup>46</sup> Although there is a lot of variation in the HLA genes, it is also important to study the non-HLA genes.<sup>18</sup> A study reported that host genetic factors polymorphisms are associated with seroconversion rate after influenza vaccine. Compared with C/T and T/T donors, persons with the IFITM3 rs12252C/C genotype had reduced seroconversion rates after vaccination.<sup>18</sup>

Although studies have been performed on the association between host genetic factor polymorphism and vaccine outcomes, this association is still in its infancy and it is hoped that more effective individual vaccines can be developed in future studies.

## 8 | THE ROLE OF IMMUNE SYSTEM IN VACCINE RESPONSE

The immune system includes innate immunity and acquired immunity, both of which are needed to control and clear viral infections. In the adaptive immune system, B, CD4<sup>+</sup> T, and cytotoxic T cells (CD8<sup>+</sup> T cells) work together to clear viral infections: B lymphocytes

synthesize antibodies and CD4<sup>+</sup> T cells are involved in cellular immunity and help B cells synthesize antibodies. CD8<sup>+</sup> T cells kill virus-infected cells.<sup>47</sup>

In fact, protective immune responses to viral infections or vaccines are usually the result of the combined action of lymphocytes. These characteristics suggest that candidate vaccines should stimulate both B- and T-cell antiviral responses.<sup>48</sup> Immunological methods for assessing vaccine efficacy are highly dependent on serological responses or antibody titers while examining T-cell responses is critical to evaluating vaccine efficacy. Influenza vaccine studies have shown that T-cell response has more correlation with vaccine protection than antibody titers in the elderly.<sup>49</sup>

The immune system varies from person to person, and the simplest reason is a large number of MHC alleles. Genetic and non-genetic factors cause variation in the immune system between people. nongenetic factors play a more important role in the variability of the immune system.<sup>50</sup>

Age, sex, and microbiota are triggers/drivers for immune system variations, which were discussed above. In addition, the immune system is formed over time through exposure to the environment, where cohabitation and chronic viral infections are responsible for diversity in the immune system. The virus affects the composition and function of immune cells, causing individual differences in the immune system. cytomegalovirus (CMV), for example, causes changes in the host immune system, and approximately 10% of all T cells in CMV<sup>+</sup> individuals can be CMV-specific. In one study, young adults with CMV infection showed a stronger immune response to the influenza vaccine, indicating a positive effect of CMV on the vaccine response.<sup>50</sup>

In short, various factors such as age, sex, genetic factors, symbiotic microbes, and pathogens lead to differences in immune responses between individuals (mentioned above), due to these variations in the immune system, people respond differently to infections and vaccines.

One study reported that 20%–50% of unexposed donors lymphocytes show considerable reactivity against SARS-CoV-2 peptides. It has been hypothesized that SARS-CoV-2-specific T cells in seronegative individuals may be derived from memory T cells originating from “common cold” coronavirus infection. More than 90% of the population are seropositive for “common cold” coronavirus. It is possible that pre-existing T-cell immunity to SARS-CoV-2 may affect the severity of COVID-19 disease. It was suspected people with pre-existing memory CD4<sup>+</sup> T cells which detect SARS-CoV-2 can have a faster and stronger immune response after exposure to SARS-CoV-2, thereby reducing the severity of the disease. In addition, pre-existing CD4<sup>+</sup> T-cell memory can also affect the vaccine response, making the immune response faster or better. In particular, pre-existing memory T cells usually lead to the development of neutralizing antibodies, which rely on the help of T cells.<sup>51</sup>

In fact, immune history is obtained over time from exposure to the virus or vaccination, this will affect the magnitude and quality of the antibody response to infectious agents in later life.<sup>52</sup> The effect of immune history on the efficacy of influenza vaccine has been established.

Exposure to influenza virus in the first decade of life will affect the antibody response during subsequent exposure to the virus or vaccine. In this case, more antibodies against the child strain will be produced. This phenomenon is called original antigenic sin, which is equivalent to immune imprinting and reflects the role of immune history in the influenza vaccine efficacy.<sup>7</sup> The shingrix vaccine is very effective (~97% efficacy) in preventing shingles and is given to people who are already infected with the varicella-zoster virus and induces a much higher antibody response than the virus infection alone.<sup>53</sup>

The impact of pre-existing immunity on the effectiveness of the COVID-19 vaccine has also been reported. One study reported that antibody response of hemodialysis patients after vaccination with BNT162b2 vaccine depends on immune status, people with a history of COVID-19 infection have a higher response to vaccines.<sup>13</sup> In line with these findings, in another study, the positive effect of a previous COVID-19 infection on the vaccine response was emphasized, this phenomenon is called hybrid immunity and is associated with high immunogenicity. Where natural immunity (after natural infection) combines subsequently with vaccine-induced immunity, resulting in 25–100 times greater antibody titers and wider cross-protection against different variants.<sup>53</sup> In hybrid immunity memory B cells and CD4<sup>+</sup> T cells work together. Actually, with the help of memory T cells, an increase in antibody response (25–100 times) is induced after COVID-19 vaccination in individuals with previous COVID-19 infection. After natural infection, immunological memory is formed. Then, after COVID-19 vaccine administration, the T-cells activate and recall the B cells, resulting in stronger and faster responses.<sup>53</sup>

## 9 | CONCLUSION

Vaccines are the most important measure for the control of infectious diseases and the COVID-19 pandemic. Two issues regarding vaccines are safety and immunogenicity. Vaccine efficacy varies between individuals. Vaccine efficacy is influenced by several factors including: infectious agent (genetic variation), vaccine factors (type of vaccine, adjuvant, dose and administration route and schedule), and the host factors including age, sex, genetics, nutritional status, gut microbiota, obesity, and immune history.

Limited studies have been performed on the effect of age, sex, BMI, and immune history factors on the efficacy of COVID-19 vaccines, and the relationship between other factors such as microbiota, host genetic polymorphism, and COVID-19 vaccine immunogenicity has not been investigated. Undersetting and modifying host causes of vaccine failure or impaired vaccine response has great value for global health.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article.

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