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VACCINATION CHALLENGES: FACTORS THAT INFLUENCE THE EFFECTIVENESS OF VACCINES

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ABSTRACT

Introduction: Although the World Health Organization (WHO) has appointed vaccination as one of the main prophylactic measures against infectious diseases, there is still a considerable number of deaths every year from vaccine-preventable diseases. These mortality data can be explained by several factors related to the effectiveness of these immunobiologicals, such as the genetics of each individual and the environment in which they live. Therefore, this work aims to point out some of these factors and discuss about them. **Methodology:** This is a literature review carried out in the following databases: Google Scholar, PubMed and WHO bulletins. **Results and Discussions:** Studies show that aspects such as genetics, sex, age and immune system diseases can interfere with the performance of immunizers, as they alter the expected response of the organism against vaccine antigens. In addition, the environment proved to be a strong influencing factor for the response against immunizing agents, being responsible for positive and negative variations in the humoral response. Malnutrition, obesity, diabetes, hypertension and psychological stress are among the factors with a negative impact on the biological production of antibodies after vaccination. **Conclusion:** Therefore, the data presented here make clear the interference of several factors for a satisfactory response to immunizers, explaining the still high rate of deaths from infectious diseases in patients already vaccinated.

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INTRODUCTION

The World Health Organization (WHO) points out vaccination as one of the main prophylactic measures against infectious diseases, which for centuries was considered the main causes of death in the world (WHO, 2020). According to the organization's data, 26% of the causes of death in 2019 were due to infectious diseases, a still significant number, but significantly lower if compared to previous decades (WHO, 2021). Two centuries after the use of the first vaccine, this approach remains extremely effective (Greenwood, 2014). With the development of new technologies in health and the elucidation of a large part of the mechanisms that allow biological protection through immunization, vaccines have evolved since then, being produced through various techniques, which include immunizers containing live attenuated or dead microorganisms, subunit vaccines (isolated antigens) and DNA/RNA vaccines. The common denominator among all of them remains the same: to generate an effective, safe and long-lasting specific immune response (Bastola *et al*., 2017). The current COVID-19 pandemic, responsible for millions of deaths in just over a year, highlighted the importance of vaccination. Due to advances in scientific research and the dedication of numerous researchers, in just one year after the WHO declaration of a pandemic status, at least five vaccines were developed to immunize the population, with variable, but satisfactory and significant efficacy rate with regard to the control of transmission and aggravation of infections (Rawat *et al*., 2020). Despite the evident success of mass vaccination campaigns, a considerable number of deaths still occur each year from vaccine-preventable diseases. Several factors related to the individual can influence the effectiveness of immunizers. One of the challenges inherent in the development of efficient vaccines is the heterogeneity of the general population, which includes not only genetic factors, but also environmental and behavioral factors (Zimmermann and Curtis, 2019). A well-documented example is the variation in the response to the tuberculosis vaccine, BCG (Bacillus Calmette-Guérin), which can be influenced by the latitude of the region where the population resides. The significant variation from 0% to 80% in the effectiveness

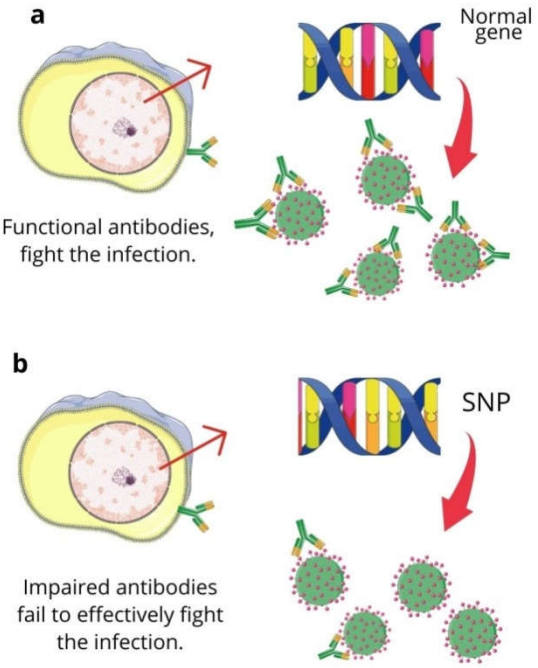
of the immunizing agent mentioned above is predominantly due to the geography of the immunization place, as shown in clinical studies, in which United Kingdom (UK) residents developed superior biological protection compared to Malawi residents, a country located in the east of the African continent (Kollmann, 2013). Many other conditions are capable of interfering with a satisfactory immune response to immunization. The aim of this review is to point out the main factors influencing the effectiveness of vaccines, in addition to identifying the most vulnerable groups, and thus evaluating the factors that can be adjusted. Understanding the population's heterogeneous immune response to immunizers is of great importance, as it can contribute to the development of new technologies for the production of more effective vaccines.

METHODOLOGY

This study is a literature review carried out through analysis of data and articles on the main factors that influence the effectiveness of vaccines and the development of immunological memory. The articles and data analyzed are published and available in databases, accessed through digital platforms such as Google Scholar, PubMed and World Healht Organization (WHO). The inclusion criteria for the selected articles were the year of publication and relevance of the topic. For this, articles published between 2011 and 2021, and WHO newsletters were used for the bibliographic survey. The descriptors used in the research were: efficacy, vaccines, immune response, factors and influence. Among the exclusion criteria, the date of publication of the articles stands out, with articles with publications prior to 2011 not being considered for the synthesis of the review.

RESULTS AND DISCUSSION

Individual Factors: The genetic diversity of individuals is a determining factor for inducing different immune responses and resistance to pathogens. Genetic polymorphism is the target of several studies that aim to understand the heterogeneous responses of the population to vaccines (Goldber andRizzo, 2015). The major histocompatibility complex (MHC) is formed by molecules with high genetic variability, since they are unique to each individual and perform, among other functions, the recognition of their own and non-self molecules, generating biological tolerance, that is, the immune system acquires the ability to not be activated by the host's own cells. The genes that encode these proteins are inserted in the system called human leukocyte antigen (HLA), often associated with genetic polymorphisms responsible for variations in the immune response of each individual (Goldber and Rizzo, 2015). Several studies have shown that variations in the class II MHC molecules are related to significant alterations in the production of antibodies in relation to the presented antigen. Single nucleotide polymorphisms (SNP) in HLA genes were associated with ineffective response to Hepatitis B vaccine, as shown in figure 1(Yucesoy *et al*., 2013). In a cohort study with 1052 individuals, researchers identified the presence of SNPs in regions of the HLA complex as responsible for an expressive variation in the levels of neutralizing antibodies after immunization against rubella (Lambert *et al*., 2015). Another cohort study evaluated the association between genetic polymorphism in genes related to follicular helper T cells and the ineffective response to vaccine against hepatitis B virus. The research revealed that the presence of SNPs in the genes CXCR5 and CXCL13 were related to the efficacy of vaccine and non-responsiveness to it (Duan *et al*., 2014). In addition to genetic polymorphism, other factors related to genetic variability may be responsible for the heterogeneous responses. Genetic ancestry defined as genetic race can have a significant impact on immunization. A survey of 2,872 individuals, including children, adolescents and young adults found that genetic ancestry influences the humoral and cellular immune response induced by the measles vaccine. The researchers found that AfricanAmerican individuals had a more expressive cellular immune response, as well as higher levels of neutralizing antibodies against measles when compared to Caucasians (Voigt *et al*., 2016).



Immunological senescence is a major influencing factor for the satisfactory response of an organism to vaccines. With advancing age, the immune system tends to work slower, taking longer to produce antibodies compared to younger individuals. In addition, these antibodies exhibit lesser neutralizing and opsonization capacity, greater self-reactivity and less specificity, especially with regard to primary immunization. In a clinical trial of primary immunization carried out with two groups, one with young adults aged between 20 and 40 years, and the other with elderly people aged over 60 years. Both groups received vaccine against hepatitis B. After the first dose, the elderly group showed a slow production of antibodies and in smaller amounts when compared to the young group, having reached equivalent numbers in antibody titers only after the third dose of the vaccine (Weinberger et. al. 2018). Interestingly, the elderly respond well to booster doses and have a satisfactory response to influenza vaccine, as shown in a survey of 205 elderly people who had seroconversion greater than 80% after influenza vaccination by the seasonal trivalent immunizer in the year 2013/14 (Narang et. al. 2018).

On the other hand, the vaccination schedule is intense in the first years of life due to the need to protect newborns and childrenthat are highly susceptible to infections. However, the presence of maternal antibodies can interfere with the response to vaccination. In a randomized clinical trial in Netherlands, the effect of vaccination against tetanus, diphtheria and pertussis in pregnant women and the antibodies levels in babies after delivery, were evaluated. The high concentration of antibodies against pertussis was observed in babies even after three months of life (Barug *et al*., 2019). This study demonstrates the need to adapt the vaccination schedule in Brazil. According to the national immunization program, the first dose of pertussis vaccine is administered at two months of age (PIN, 2021). Still in relation to the genetics of individuals, biological sex was also pointed out as an important variant to be considered in relation to the immunization process. Several studies have shown that women are more reactive to vaccination than men, with higher production of antibodies and also a higher incidence of adverse reactions. A survey with 5,291 college students conducted between 2004 and 2017 evaluated the long-term response to the hepatitis B virus vaccine in men and women. The researchers identified an increase of 20% in serum antibody levels in female volunteers when compared to male ones (Trevisan *et al*., 2020). A challenging factor for any immunizer is the diverse genetic conditions that directly affect the action of the immune system. Primary immunodeficiencies, sickle cell disease (SCD), thalassemia, autoimmune diseases, among others, directly influence immunity and, therefore, the effectiveness of a vaccine in a given individual. Many of these conditions can remain undiagnosed

for a long time and inadvertently affect a patient's immunization. It was demonstrated through a study with 72 individuals with SCD and 30 healthy individuals (control group) immunized with the tetravalent influenza vaccine, that participants with SCD had seroconversion rates, immune cell counts, mainly T and B lymphocytes and memory cells greatly reduced when compared to the control group, illustrating the need for personalized monitoring of this group with regard to immunization (Negant *et al*., 2019).

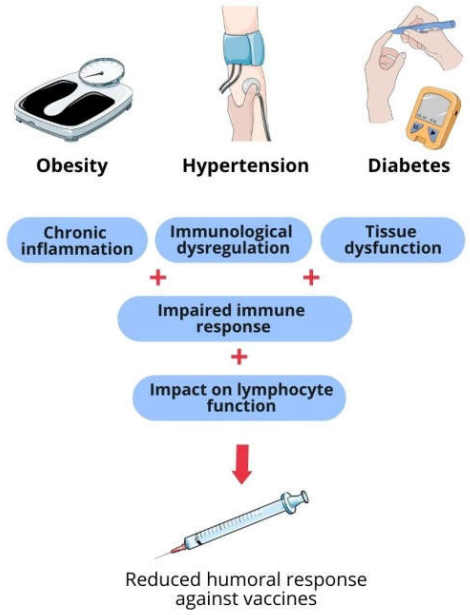
Environmental Factors: Similar to genetic heterogeneity, the diversity of the environment that the individual is exposed to is crucial to the function of the immune system and consequently impacts the effectiveness of vaccines. During the first years of life, exposure to the outside world is essential for a satisfactory development of the immune system(MacGillivray and Kollmann, 2014). Primarily, geographic location has an unexpected impact on vaccine effectiveness, and many factors are linked to this. The latitude is closely related to sun exposure and climate, both associated with variation in the effectiveness of some immunizers, such as the BCG vaccine, in which performs better in colder climates with higher latitudes (Kuan *et al*., 2020). An epidemiological study that evaluated the efficacy of the multivalent pneumococcal conjugate vaccine (PCV7), with data from day care centers in Portugal, Norway, France, Greece, Hungary and Hong Kong, pointed to a variation in the response of the vaccine in relation to theclimate, where PCV7 showed better performance in colder regions (Gjini, 2017). Exposure to sunlight must also be taken into account, as ultraviolet radiation is related to vitamin D synthesis. Although it is mainly linked to calcium regulation in bone tissues, vitamin D has also been associated with the proper functioning of the immune system, both innate and adaptive (Mailhot and White, 2020). Present in most cells of the immune system, the vitamin D receptor is related to the suppression of adaptive immunity, since it is able to switch between Th1 and Th2 immune response patterns in helper T lymphocytes, triggering immunoregulatory responses (Goncalves-Mendes *et al*., 2019). A prospective cohort study of 447 adults evaluated the response to vaccination against hepatitis B in relation to the blood levels of vitamin D of those immunized. The research showed that participants with lower levels of vitamin D had a less satisfactory response compared to those with normal serum levels. In addition, researchers also noted that the vaccine exhibited more effective response when administered in the summer, when serum levels of vitamin D were higher in participants, compared to those immunized during the winter (Kashi, et. al., 2021).

In parallel, a study with 173 men aged between 18 and 25 years evaluated the influence of serum levels of vitamin D and antibodies titers after HPV vaccination. In contrast to the result discussed above, this study showed that antibodies titers were higher for all strains of the virus among participants with lower levels of vitamin D (Zimmerman, et. al., 2015).Other studies have shown that vitamin D has a very varied role according to the type of immunizing agent used, highlighting the need for further studies to clarify this interaction (Goncalves-Mendes *et al*., 2019). Another factor related to the environment is the exposure to endemic or seasonal infections typical of the local ecosystem. It is a fact that pre-existing infection or antibodies produced by previous infections can affect the performance of a vaccine, especially with regard to vaccines containing live attenuated microorganisms (Mok and Chan, 2020). A phase II randomized clinical trial with 300 children in Bangladesh evaluated the pre-existing immunity as an influencing factor in the performance of a live attenuated influenza virus vaccine. The study showed that children without markers of pre-existing immunity had a better response to the immunizing agent used (Brickley *et al*., 2019). On the other hand, pre-existing immunity can positively affect the individual, depending on the pathogen of interest. A recent study with 86 volunteers (59 of these seronegative for the virus and 27 seropositive) evaluated the response to vaccination against SARS-CoV-2 by the Sputnik V vaccine. All seronegative individuals developed a strong humoral (IgG) response after the second dose of the vaccine, while seropositive individuals showed an increase of 40% in the serum antibody levels soon after the first dose (Claro *et al*., 2021).

Behavioral Factors: Factors unrelated to genetics and the environment can also impact an individual's organism in different ways. The immune system is subject to the influence of habits that depend on behavior and daily practices of the patient, such as eating, which can lead to malnutrition, energy imbalance and other health complications; and psychosocial factors, such as the use and abuse of legal and illegal drugs, which act in the body through different mechanisms of action. The role of nutrition goes beyond just being a source of energy for the maintenance of the body's systems, it is through it that various components necessary for the proper functioning of the body are acquired, such as vitamins and minerals that play essential roles in maintaining homeostasis (Calder *et al*, 2020). Nutritional status at the time of vaccinationmayinfluence the effective response to a vaccine. Malnutrition and poverty have been associated with a poor response to immunizations in children receiving oral vaccines. In developing countries, the performance of these immunizers is considerably lower when compared to developed countries, where rates of social problems are lower (Church *et al*., 2018).A prospective observational study with 700 infants in a Bangladeshi slum evaluated the efficacy of oral polio and rotavirus vaccines. The researchers identified environmental enteropathy (subclinical inflammation accompanied by malabsorption and recurrent bowel dysfunction in poverty-stricken regions) in 80% of the participating volunteers, and 28% were also malnourished. The study showed that 20.2% did not respond to the polio vaccine and 68.5% did not respond to the rotavirus vaccine (Naylor *et al*., 2015). Micronutrient deficiency also significantly interferes with the immune system, as discussed above about the influence of the Vitamin D. Vitamin A is related to the function of several cells of the immune system, and its deficiency has already been identified as harmful to the immunization process. A randomized clinical trial with pregnant women assessed whether vitaminA supplementation in pregnant women could influence the effectiveness of the H1N1 vaccine in both mothers and infants. The study demonstrated an increase in the response to vaccination of mothers, without interfering with the response in babies (Ahmad *et al*., 2018). Similarly, a blinded randomized placebo-controlled clinical trial in Bangladesh looked at the effect of vitamin B12 supplementation in pregnant women immunized against H1N1. Similar to the previous study, the researchers demonstrated that the vaccine response of mothers who received the supplement was superior to the placebo-treated group; in babies, vitamin B12 supplementation did not change antibody levels, however, it reduced the inflammatory response (Siddiqua *et al*., 2016).

Another micronutrient of great relevance for the functions of the immune system is the iron, present throughout the body and imperative for several metabolic processes that guarantee homeostasis. Individuals with low serum iron concentrations have a low humoral immune response (antibody production) compared to those with normal levels. Furthermore, this mineral is of great importance for proliferation of B lymphocytes, which are the cells responsible for the production of immunoglobulins (Jiang *et al*., 2019). In a cohort study with 303 infants in Kenya, researchers found that iron deficiency caused less effective immunization against whooping cough, diphtheria and pneumococcus. The same team assessed the impact of iron supplementation at the time of vaccination, and those who received the supplement exhibited higher production of antibodies against measles (Stoffel *et al*., 2020). Likewise, zinc is a mineral with great importance for immune functions, and its deficiency is related to cellular dysfunction in both innate and adaptive immunity. Despite this, the role of zinc in the immune response during immunization is still controversial. A study in Bangladesh evaluated the immune response to tetanus vaccine in individuals with low levels of vitamin D and zinc; the results indicated low serum levels of zinc as a positive factor for the response against the vaccine in question (Das *et al*., 2021). In parallel, another double-blind and placebo-controlled randomized clinical trial with 620 infants in India found no significant increase in the immune

response of these infants immunized against rotavirus after zinc supplementation (Lazarus *et al*., 2018). Just as malnutrition can lead to immunological alterations and dysfunctions, the energy imbalance caused by high caloric intake has its impact on the homeostasis of the immune system. Obesity, mainly caused by the accumulation of fat, is associated with a state of low-grade chronic inflammation in the body, causing tissue dysfunction, secretion of pro-inflammatory mediators and alterations in lymphocyte functions. When associated with metabolic syndrome (MS) and insulin resistance, it causes a state of immune dysregulation, with deficiency mainly in the adaptive immune response and consequently in the functions of lymphocytes, resulting in low antigen presentation and reduced activation of B lymphocytes for plasma cells, which are producers and secreters of immunoglobulins (Andersen *et al*., 2016). The increase in body mass index (BMI) is directly related to the lower success of vaccination against hepatitis B, mainly due to chronic inflammation associated with high concentrations of pro-inflammatory cytokines and B lymphocyte dysfunction in these patients (Liu *et al*., 2017). Overweight is also observed as a determining factor for the development of influenza, even after vaccination, as shown in a prospective observational study with the inactivated trivalent influenza vaccine with 1022 adult volunteers. After vaccination, the obese study population was twice as likely to develop flu or a similar illness compared to volunteers with normal BMI (Neidich *et al*., 2017). Although hyperglycemia, present in diabetes mellitus (DM), provides greater susceptibility to the development and aggravation of infections, the relationship between high blood glucose concentrations and the effectiveness of vaccines is still poorly understood. Occasionally, DM is considered responsible for the superficial dullness in the response to the vaccine against hepatitis B, however, the mechanisms still need to be clarified (Verstraeten *et al*., 2020). A recent observational cohort study with 509 patients diagnosed with COVID-19 showed that DM did not affect the production of antibodies against the virus, although the condition has been identified as a determining factor for an unfavorable outcome of the disease(Lampasona *et al*., 2020). A summary of the effect of obesity, hypertension and diabetes on the biological processes of immunization can be seen in Figure 2.



Integrating the scope of comorbidities associated with obesity, hypertension and cardiovascular diseases are related to an unsatisfactory response to vaccination. A survey of 86 patients immunized against COVID-19 with the Pfizer/BioNTech vaccines showed that obese and hypertensive patients exhibited lower serum antibody levels when compared to healthy patients. The same study also pointed out smoking and dyslipidemia as factors causing a decline in plasma levels of immunoglobulins (Watanabe *et al*, 2021).
Still, in relation to mental health, emotional stress has also been pointed out as an important factor with regard to the development of effective immune responses in immunization processes. Cortisol, released during emotional stress, has an immunosuppressive effect and can affect several pathways of the immune response, causing, for example, a reduction in the activity of T lymphocytes and consequently affecting the activation of B lymphocytes, which are cells with a decisive role in the response against vaccines (Hayward *et al*., 2020). In addition, melancholy and suffering have also been linked to poor immune response against various types of vaccine; in addition, the melancholy state itself can indirectly cause other problems, such as eating disorders, leading to immunodepression and increasing the body's susceptibility to the action of microorganisms (Madison *et al*., 2021). A double-blind randomized controlled trial with 306 participants evaluated the cortisol stress response in children vaccinated with Bacillus Calmette-Guérin (BCG), tetanus toxoid, hepatitis B virus and oral poliovirus vaccines. This study demonstrated that elevated cortisol was associated with lower circulating T-cell counts and lower responsiveness to the delayed-type hypersensitivity skin for BCG, corroborating with the results of the aforementioned study, which points to cortisol as an agent suppressor of the immune response against vaccines and infections. These data show the need for mental health care and its influence on the body's homeostasis and defense (Huda *et al*., 2019).

CONCLUSION

The data here presented make clear the interference of several factors for a satisfactory immunization, which may explain the still high rate of deaths from vaccine-preventable diseases. Individually, genetics, sex, genetic ancestry, age and some diseases can interfere with the effectiveness of an immunizing agent, in addition to aspects related to the environment in which the individual lives, with climatic conditions and even exposure to sunlight capable of causing variations in the body's immune response. In addition, lifestyle proved to be very influential, with socioeconomic, behavioral and even psychological factors capable of blunting the immune system's performance in immunization. Therefore, since vaccines are still the main prophylactic measure against infectious diseases in the world, understanding all the processes involved in the biological response against these immunizers is extremely important, since several of these factors can be adjusted, improving the effectiveness.

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