Gauging effectiveness of Covid-19 vaccines with immunological markers and booster doses

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WORD COUNT	4765	TIME SUBMITTED	09-MAY-2024 05:04PM
		PAPER ID	108859734

TYPE OF ARTICLE: Reviews

Gauging effectiveness of Covid-19 vaccines with immunological markers and booster doses

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ABSTRACT

Objectives. This review seeks to highlight the importance of monitoring vaccines performance through immunological markers and number of doses required for effectiveness. With the sudden emergence of COVID-19 disease and associated health consequences came the introduction of the hastily developed vaccines against the SARS-CoV-2 virus. Initial monitoring of COVID-19 immunization trial participants revealed an

increase in risk of new infections. To curb the high mortality from COVID-19, booster doses were introduced.

Methodology. The methods utilized in this research comprised material collecting, screening, analysis, and rating literature from PubMed/Medline, Scopus, and Embase databases using relevant keywords. The search was restricted to studies published up until May 2023. There were systematic reviews, narrative reviews, and other types of review studies that looked at the efficacy of the several COVID-19 vaccines. The procedure entailed integrating existing information, summarizing findings, and documenting reliable data for approving vaccination efficacy.

Result. Following the initial vaccination, a booster dose is utilized to re-expose the immunizing antigen to restore protective levels of immunity to that antigen following a decline in memory of initial exposure. This demand became heightened in the case of COVID-19 by the diverse pathologies observed. COVID-19 diagnosis, etiology, and severity have been connected to ten to fifteen neutralizing epitopes within and outside the receptor-binding region that are targeted variably by human polyclonal antibodies. Antibodies against the viral spike glycoprotein's receptor-binding domain (RBD) develop within the first three weeks after symptoms appear, with IgG and maybe IgA seroconversion occurring sequentially or simultaneously with IgM.

Conclusion. For novel infectious diseases, monitoring immunological markers are crucial for assessing vaccination effectiveness. So far, the immunological markers studied have undoubtedly aided in understanding the pathogenesis of COVID-19, its vaccines effectiveness and success rate. Recipients of the vaccine, particularly those fully immunized but with poor immunological response, should receive a second dose.

Key Words: COVID-19, Immunological-markers, Booster-doses, Vaccine

INTRODUCTION

The COVID-19 global pandemic claimed many lives, and public health, food systems, and workplace were all threatened.

SARS-CoV-2, a highly virulent and invasive virus discovered in 2019, was responsible for the severe respiratory disease afterwards termed COVID-19, which became a pandemic. Though its true origin, whether natural or engineered, has been debated, though linked to the Huanan South China seafood market [1].

The global health community prioritized prevention, treatment, and stopping the spread of the virus, with nothing less than a complete halt or reduction in the disease's consequences regarded economically and socially devastating. Remdesevir, a previously developed antiviral drug used to treat hepatitis C and then Ebola fever and Marburg virus, rose to prominence during the pandemic after the US Food and Drug Administration (FDA) approved its use in COVID-19 patients [2,3]. In addition, lockdowns [4] and other physical measures were put in place to halt the infection's fast spread, and eventually, vaccination against the illness - as is typical in such outbreaks, epidemics, or pandemics, became a highly efficient COVID-19 preventative strategy.

Innate and acquired immune responses, both of which entail varying chemo-tactic agents; the cytokines, are the two basic modes of action for the immune system. The molecular weights, shapes, functions, cells involved in their secretion, and targets of various cytokines, vary. Various levels of cytokines are produced depending on the infection, which may result in pathogen clearance and inflammation. The innate immune response triggers the production of cytokines, which activate the adaptive immune response which comprises humoral (B-lymphocytes) and cell-mediated (T-lymphocytes: both CD4+

helper T cells (Th) and CD8+ cytotoxic T cells (Tc)) immunity [5]. The innate response causes infected cells to generate interferons (IFNs) and many pro-inflammatory cytokines during viral infections such as SARS-CoV-2 infections. IFNs signal neighboring uninfected cells that an antiviral strategy is required [6]. The cytokines also stimulate adaptive response CD4+ T lymphocytes, which cause B-lymphocytes to produce specific neutralizing antibodies against the virus, and CD8+ Tc cells, which cause virally infected cells to undergo programmed cell death [7]. The timing of both innate and adaptive immune responses is critical. In other cases, after encountering the innate response, the virus causes a delay in the production of IFNs [8]. This delay frequently results in an unrestrained increase in viral load, rendering the adaptive response inefficient in adequately fighting the infection. A delay in IFN synthesis may cause the release of cytokines such as IL-6, IL-8, IL-12, TNF, IL-17, IFN-, IL-10, C-reactive proteins (CRP), D-dimer, and ferritin [5]. As a result, the severity of the illness, including inflammation and its consequences, worsens. A decrease in the number of natural killer cells, B and T cells, monocytes, eosinophils, and basophils (lymphopenia) has also been observed in very ill patients, resulting in a delay in viral clearance [9]. Magro, *et al.* [10] had observed substantial deposits of terminal complement components C5b-9 (membrane attack complex) as well as C4d in research comprising five cases of skin and lungs of COVID 19 patients.

This review intends to highlight the significance of measuring vaccine efficacy, particularly in emergency scenarios such as COVID-19, utilizing relevant immunological indicators and vaccine dosages. As a result, the study advances the science of vaccine development and vaccination.

Methodology

The methods utilized in this research comprised material collecting, screening, analysis, and rating literature from PubMed/Medline, Scopus, and Embase databases using relevant keywords. The search was restricted to studies published up until March 2022. There were systematic reviews, narrative reviews, and other types of review studies that looked at the efficacy of the several COVID-19 vaccines. The procedure entailed integrating existing information, summarizing findings, and documenting reliable data for approving vaccination efficacy.

COVID-19 Vaccine Types and How They Work

With the idea that vaccination could potentially stop the spread of the virus, a COVID-19 vaccine became necessary. This realization fueled the global scientific and medical community's urgent efforts to develop a vaccine against the disease and use the envisioned vaccines to reduce, if not completely stop, virus transmission.

There were a few twists and turns though in the development of the COVID-19 vaccines that demanded thorough assessment and monitoring of immunological responses to the vaccines in individuals who have had it. Beyond the laboratory, some opinions, from the start of the vaccine's use, held that people's lack of trust in the vaccines came from the belief that the vaccines were not methodically and scientifically designed. The emergence of new variants that appear to be more transmissible and resistant to initial antibodies to the original strain, further slowed progress in controlling the pandemic [11].

Following the manufacture of COVID-19 vaccines, the European Union approved use of the mRNA vaccines; Tozinameran from BioNTech and Pfizer, Moderna's mRNA-1273

vaccine, and AstraZeneca's vector vaccine AZD1222. All three vaccines became immediately available for use and showed high efficacy in ensuing clinical studies [12]. The need for booster doses became crucial soon after these vaccines were introduced. Before that, it was necessary to understand when and how these vaccines should be given, as well as whether they should be given in a single dose or in a series of boosters.

Long-term follow-up on vaccine trial participants revealed an increasing risk of new infections, an observation that is consistent with the conventional belief that antibody levels drop with time following vaccinations. Published vaccination results, revealed that while the COVID-19 mRNA and viral vector vaccines effectively prevented clinically significant disease, virus transmission continued in both mRNA and vector vaccine immunizations. However, this was more noticeable with viral vector vaccine vaccinations [13]. These findings, along with reports on patients with immunocompromised conditions, was what prompted the FDA to issue emergency use authorizations (EUAs) for both the Pfizer-BioNTech COVID-19 vaccines and the Moderna COVID-19 vaccine in patients with immunocompromised conditions and for all adults on November 19, 2021 [14]. Accordingly, the Centers for Disease Control and Prevention (CDC) recommended on September 24, 2021, that a booster dose for any mRNA COVID-19 vaccine be given at least six months after the second dose of any mRNA COVID-19 vaccine. This further justified the intense studies into the disease's immunological markers to act as indicators of vaccine efficiency or success rate based on antibody production prior to and after booster doses.

Both the Pfizer-BioNTech and Moderna vaccines use mRNA to transmit a message to the immune system, ordering the cells to produce a harmless portion of a particular spike

protein identical to that seen on the surface of SARS-CoV-2. The harmless spike protein is identified as foreign by the human body, and antibodies are produced against it. After the mRNA has served its purpose, it degrades and is flushed out of the system within hours.

The mRNA vaccine technology is relatively new. The efficacy of the Pfizer vaccine was initially studied in around 44,000 volunteers over the age of 16 in locations where COVID-19 was already prevalent [15]; clinical trials have repeatedly showed high efficacy across all age groups, genders, races, ethnicities, and those with underlying medical conditions. After two doses of the Pfizer vaccine, more than 9 out of 10 people were protected against COVID-19, regardless of age or health status. The first dose primes the immune system, but protection is only temporary since antibody levels drop. A second dose boosts antibody levels, allowing the immune response to mature and last longer. Clinical investigations demonstrated that after the second dosage, the Pfizer vaccine was more effective against symptomatic COVID-19 infection.

The viral vector vaccine, administered in a single shot, is manufactured by Johnson & Johnson's Janssen Pharmaceuticals Companies. Viral vector vaccines use a modified version of another virus as the vector to transmit the essential instructions, much as live coronavirus targets human cells. The virus infects a cell in the body and exploits its machinery to make a virus fragment (spike protein) that causes COVID-19. The spike protein emerges on the cell's surface and is recognized as foreign by the immune system.

Immunological Markers and Booster Dose Effectiveness of COVID 19 Vaccines

While booster doses of a vaccine may be required, it is important that policy decisions regarding vaccine booster doses should be based on evidence of individual and public

health benefit, as well as the desire to meet and ensure global equity in vaccine availability, as in the case of COVID 19 vaccines [16]. In other words, even while the WHO has on occasion advised the necessity for booster doses, they shouldn't be given solely on the grounds that they are the only method to prevent the disease because there may be risks [17], the majority of which are still not entirely understood. Regardless, the increased usage of booster doses is typically predicated on reports of falling antibody levels shortly after the initial vaccination. According to Feikin *et al.*[18] the effectiveness of the COVID-19 vaccine was reported to have dropped between 1 month and 6 months in people of all ages by 21.0 percentage points (95 percent CI 13.9-29.8) and by 20.7 percentage points (10.2-36.6) in adults over the age of 50. The same study also revealed that for COVID-19 disease with symptoms, vaccine effectiveness decreased by 24.9% (95 percent CI: 13.4-41.6) in people of all ages and by 32.0% (11.0-69.0) in older people, while for severe cases, vaccine effectiveness decreased by 10.0% (95 percent CI: 6.1-15.4) in people of all ages and by 9.5% (5.7-14.6) in older people. The World Health Organization's "Interim Recommendations" for some vaccines, such as the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm, on those aged 60 years or older, agreed with findings on the need for an additional third dose [19] as part of the primary series to help make initial immunity more robust. Based on these reports, some regulatory organizations then suggested COVID-19 booster doses for BNT162b2, mRNA 1273, and Ad26.COV2.S, and so they were included in the product labels. There have been recommendations for using both homologous and heterologous booster regimens [20], all of which were aimed at producing quick results that could aid in the pandemic's containment.

Vaccination's success is determined not only by the type of protection it provides against active illness, but also by the immunological markers it produces. Many of the existing COVID-19 vaccinations were successful. Immunological markers associated with these vaccines were often identified by comparing published vaccine efficacy statistics with data from rigorous studies that examined immune responses following immunization [21]. Several investigations have found that the presence of virus-blocking 'neutralizing' antibodies is an accurate predictor of vaccine effectiveness. Vaccinations that elicit high levels of virus-blocking neutralizing antibodies, such as those developed by Pfizer–BioNTech and Moderna against COVID-19, appeared to be more successful than those developed by Oxford–AstraZeneca and Johnson & Johnson [22]. In a study, immune responses of 171 breakthrough cases were compared to those of approximately 1,404 patients who received the vaccine but did not develop symptoms: participants with higher levels of neutralizing antibodies as well as 'binding' antibodies, which detect the SARS-CoV-2 spike protein, were better protected from symptomatic infection, though not completely [23]. The researchers utilized a model to calculate antibody levels that corresponded to different levels of COVID-19 vaccine protection in trials, ranging from 50% to 90%. It was claimed that other vaccines that produce similar antibody responses should provide identical protection against symptomatic diseases.

Immunological markers are proteins that help the body protect itself against microbial infections and other external substances. In the case of SARS-CoV-2 infections, antibodies against the viral spike glycoprotein's receptor-binding domain (RBD) develop over the first three weeks after symptoms appear, with IgG and maybe IgA seroconversion occurring sequentially or concurrently with IgM [7].

According to Secchi *et al.*[24], anti-RBD IgG was detected in 95 percent of COVID-19 patients tested four weeks after symptoms appeared using the Luciferase Immunoprecipitation System (LIPS), with high antibody levels observed at follow-up until the third month leading to hospital discharge. In a similar study, anti-RBD IgG and anti-spike IgA were also linked to patient survival and lower SARS-CoV-2 RNA persistence in nasopharyngeal swabs. Antibodies targeting the RBD of the spike glycoprotein have been shown to reduce viral load in patients with mild-to-moderate COVID-19 infection: virus clearance was demonstrated by neutralizing titers achieved with REGN-COV2; greater than 1000 times the titers achieved with convalescent-phase plasma [25]. Furthermore, anti-spike neutralizing antibodies (nAbs) from COVID-19 patients have also been found to inhibit viral reproduction *in vivo* with decrease in viral infection in human cells *in vitro* [26]. HIV-1 pseudotypes and plasma selection experiments with vesicular stomatitis virus/SARS-CoV-2 chimaeras5 were employed to demonstrate that multiple neutralizing epitopes, within and outside the receptor-binding domain, were variably targeted by human polyclonal antibodies [27].

The need to carefully examine, the nature and quality of the memory B cells that would be required to produce antibodies upon reinfection has not been examined as observed from studies on the humoral memory response in a cohort of 87 individuals assessed at different periods after infection with SARS-CoV-2. which showed that titres of IgM and IgG antibodies against the RBD of the spike protein of SARS-CoV-2 decreased significantly over a 1.3 and 6.2-months period, with IgA being less affected [28]. The study further showed that concurrently, neutralizing activity in plasma decreases by five-fold in

pseudotype virus assays and that by contrast, the number of RBD-specific memory B cells remains unchanged at 6.2 months after infection.

In the absence of immunization, antibody reactivity to the SARS-CoV-2 RBD, neutralizing activity, and the number of RBD-specific memory B cells remained relatively stable between 6 and 12 months after infection[7]. Vaccination, on the other hand, boosts all components of the humoral response, resulting in serum neutralizing activities against similar variants of concern (VoC) that are comparable to or greater than the neutralizing activity achieved by vaccination of naive individuals against the original Wuhan Hu-1 strain.

A variety of methods can be used to decide when a booster dose is required, one of which is to measure the level of disease-specific antibodies a few years after the original dose [29]. Anamnestic response, or the rapid generation of antibodies in response to an antigen stimulus, is a well-established approach for assessing the requirement for a booster dose of a specific vaccine. If the response to the initial vaccine dosage remains high after a few years, a booster dose may not be required. COVID-19's immunological response has been measured by assessing antibody levels in the bloodstream and how well they neutralized the virus in laboratory experiments. Another way for evaluating the requirement for a booster dosage is to estimate active B and T cell activity against that antigen following first immunization, or to establish illness prevalence in vaccinated populations[30]. A booster dose of COVID-19 mRNA vaccine can be administered at least 28 days following the second dose of the same vaccination, according to guidelines [17]. When COVID-19 immunizations were first used, the CDC recommended only one booster dose of the mRNA vaccine whereas immunocompromised patients who had received the

J&J/Janssen COVID-19 vaccination were not required to receive a booster dose. This was because there wasn't enough evidence to suggest if immunocompromised persons who got the J&J/Janssen vaccination would have a significantly enhanced immune response after getting a booster dose of the same vaccine [17]. This indicates that not all vaccines, in this case COVID-19 vaccines, necessitate booster shots.

However, it is generally accepted that cases involving immunocompromised persons appeared to fall within the unusual conditions that could necessitate COVID-19 booster dosages. For target groups (immunocompromised populations) particularly solid organ transplant recipients, patients with cancer, haematological malignancies, and dialysis patients, as well as those with risk factors for non-response, such as the elderly, use of corticosteroids, immunosuppressive medications, or anti-CD20 agents where the immune response rate after the vaccine's conventional main series is deemed insufficient, extra doses may be required as part of an extended primary series [31,32]. An additional dose in the first series is given to boost the immune response and build a high level of disease resistance.

Conclusion

The development of high-avidity antibodies in convalescents and repeated vaccinations should be of utmost importance in assessing the efficacy of against COVID-19 and similar infectious diseases. A stronger infection-neutralization capability against SARS-CoV-2 VoCs, particularly those with immune escape properties, should evolve over time following a about three spike antigen exposures [19]. Additionally, a single SARS-CoV-2

infection does not provide the same level of protection as an infection and vaccination in combination. In all therefore, triple-vaccinated naive individuals could achieve nearly the same level of neutralization capacity against the immune escape VoC Omicron as vaccinated convalescents, as well as individuals who had a breakthrough infection with either the Delta or the Omicron VoC.

Regrettably, due to dramatic turnarounds, this disease was and remains a substantial health risk with diverse and disproportionate impact on people and communities. The introduction of vaccines to combat the pandemic was not without challenges, even though these vaccines were designed with the intention of restoring hope to the world. Regardless of the noble intentions, they received a mixed response from anti-vaxxers who then, believed that the vaccine was not thoroughly assessed and reviewed. Diverse reports and experiences based on data on COVID-19 vaccine usage were not uncommon with immunizations, particularly ones hurried for human use. The reactions ranged from "low-grade fever, weariness, headache, and bodily pains" to "discomfort at the injection site." However, overall experience remained good. Additionally, earlier adverse reactions related to “cytokine storm” which were reported due to the disease before the introduction of the vaccines, later waned very considerably.

Booster doses were originally intended to be given six months after the last dose of the Pfizer and Moderna vaccines but were later extended to all adults; to be taken six months after their second dosage of either of the mRNA vaccines, and six months after the first dose of the viral vector vaccines. The goal was to ensure that the immune boosters dramatically increased people's immunity. Due to concerns about the vaccine's efficacy

after initial inoculation, these were quickly recommended to boost protection, particularly in the immunocompromised, such as those on cancer treatment medications.

With the emergence of the Omicron variant, any doubts about the need for COVID-19 vaccine booster injections were erased. Overall, COVID-19 vaccines booster doses were essential since the immunity produced by the initial dose of vaccinations tended to wane quickly afterward, exposing individuals to viral reinfection.

The effectiveness of vaccine boosters has always been determined by the immune system's response. The use of immunological markers to track the efficacy of COVID-19 vaccinations has been a success, especially in terms of antibody production against the virus. Doubtless, progress toward pandemic control is hampered by the introduction of variants that appear to be more transmissible and immune-resistant. More than 10 to 15 markers, including hematological (increase in lymphocyte count, neutrophil count), inflammatory (C-reactive protein (CRP)), and immunological interleukin (IL)-6 markers, especially those related to acute respiratory distress syndrome (ARDS) and antibody production, have been successfully used in COVID-19 to understand the performance of the vaccines [33].

From the original Alpha to Beta, Gamma, Delta, and Omicron, SARS-CoV-2 mutated into several types of concern. Some of these were viewed as being extremely essential because of their enhanced transmissibility[34], higher virulence, or decreased vaccine efficacy[35]. The COVID-19 pandemic may persist because of these alterations.

The benefit in use of booster doses is especially true for individuals who have been fully immunized but have an impaired immune system. Given the typical loss of immunity

following initial exposure, even in the immunocompetent, such individuals stand to benefit considerably from COVID-19 vaccine booster doses. Even though COVID-19 immunizations are effective in preventing severe disease, studies have revealed that their efficiency in preventing infection or severe illness declines with age, especially in people aged 65 and over. The emergence of the Omicron form further underscored the importance of COVID-19 vaccine boosters. There is no question therefore, that COVID-19 booster injection enhanced immune response; evidenced by several reports[36]. As a result, we can conclude that if people's immune systems respond better and they receive the immunization, especially a booster, they should be better protected against highly transmissible infections like COVID-19.

Declarations

- **Ethics approval and consent to participate** (Not applicable)
- **Consent for publication** (Not applicable)
- **Availability of data and material (**Not applicable**)**

Competing interests

We the authors of the manuscript "**Gauging Effectiveness of Covid-19 Vaccines with Immunological Markers and Booster Doses"**, declare that there is no conflict of interest arising from this work as stated herein:

1. That there exists no third-party financial support for this work in the submitted manuscript.

2. That there are no financial relationships with any entities that could be viewed as relevant to the general area of the submitted manuscript.

Funding

We the authors declare that:

1. No funding was received for this work in the submitted manuscript.
2. That no payments were made to the authors, or to our institutions on our behalf.

Authors' contributions

Conceptualization, Emenike Onyebum **Irokanulo**[1].; data curation, Emenike Onyebum **Irokanulo**[1].; Bibianna Omo-ovbiye **Egharevba**[2a]**.;** writing—original draft preparation, Bibianna Omo-ovbiye **Egharevba**[1].; writing—review and editing Emenike Onyebum **Irokanulo**[1]**.;** Charles Obiora **Nwonuma**[2b]**.** All authors have read and agreed to the published version of the manuscript.

Acknowledgements (Not applicable)

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