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Title: A Comparative View of COVID-19 Vaccination and the Aging Immune System

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A Comparative View of COVID-19 Vaccination and the Aging Immune System

Background

As we age, our bodies become less capable of fighting infection, so our immune systems do not respond to vaccinations as well as they ought to. Overall, the mRNA vaccines now available (mRNA-1273 and BNT162b2) appear to be successful. However, vaccination-induced protection wanes more quickly in many elderly persons, and their immune responses are weakened. Clinicians can prioritise older individuals since they are more likely to experience clinically meaningful outcomes due to their elevated risk of severe COVID-19.

Methods

Conducted a narrative review of the literature from 2020 to 2025 using the PubMed and Scopus databases to identify the studies and included clinical trials, observational cohort studies and mechanistic studies that evaluated immune responses and clinical outcomes according to age.

Results

In clinical trials, it generated strong neutralizing antibody and C.D.4+ T-cell responses across age groups. All the older adults had lower antibody levels and weaker T-cell responses. And despite considerable debate over the vaccine's efficacy, there is now considerable population data suggesting it continues to protect against severe disease (once boosters are given and updated).

Conclusion

At the same time, with age, both the magnitude and duration of protection against SARS-CoV-2 infection after vaccination slowly decline. The vaccine may not protect older adults from getting serious illness. To do this, they should use age-appropriate vaccine technology to provide safe, durable, and superior immunity in older adults.

Keywords

Immunosenescence, SARS-CoV-2, mRNA, Vaccines, Immunity

Introduction

The intricacy of immune responses generated by vaccinations has gained considerable attention as a result of the COVID-19 pandemic, particularly given the continually shifting viral strains. Early vaccine evaluation focused mostly on antibody-mediated (humoral) immunity, although it is now clear that this is only one component of protective immunity. T cell-mediated immunity is crucial for controlling infection and reducing illness severity, according to a growing body of data, especially when neutralizing antibody levels progressively decline (Sallusto et al., 2022; Sette & Crotty, 2021). Unlike antibodies, which primarily prevent viral entrance, T cells aid in the elimination of infected cells and support the coordination of the complete immune response.

The COVID-19 pandemic has brought attention to the complexity of vaccine-induced immune responses, especially in light of the constantly changing viral strains. Initial vaccination evaluations focused mostly on antibody-mediated (humoral) immunity, but it is now evident that this is only one aspect of protective immunity. As neutralizing antibody levels gradually decrease, an increasing amount of research indicates that T cell-mediated immunity is essential for managing infections and lessening the severity of sickness (Sallusto et al., 2022; Sette & Crotty, 2021). Unlike antibodies, which mainly prevent viral entry, T cells help eliminate infected cells and coordinate the entire immune response.

T cell-mediated immunity's function in immunological memory is another crucial component. Even when circulating antibody levels decline, memory T cells can continue to exist for long stretches of time and react quickly when re-exposed to the virus, helping to maintain protection. Research has demonstrated that T cell responses specific to SARS-CoV-2 can be detected months after vaccination or spontaneous infection, underscoring their significance in long-lasting immunity (Dan et al., 2021). This persistent cellular memory is especially important when considering booster shots and the continuous evolution of viruses.

In addition to age, comorbidities have an impact on immunological response. Chronic illnesses such as diabetes, heart disease, obesity, and long-term respiratory problems are associated with immune dysregulation and persistent low-grade inflammation. This condition, which is frequently called "inflammaging," might hinder T cell activation and proliferation as well as innate and adaptive immune responses (Franceschi et al., 2018). People with many comorbidities may therefore not react to immunizations as well as they should, increasing their risk of infection and the implications of a catastrophic illness.

All things considered, these results demonstrate how crucial it is to understand the immune systems associated with vaccination, especially in vulnerable populations. Understanding immunological mechanisms and the changing effects of age and comorbidities on the immune response is necessary to develop a viable treatment against COVID-19.

Materials and Methods

Study Design and Population

In their initial study, Dietz et al. (2023) employed a longitudinal observational approach that allowed for the evaluation of immunological responses at different times after SARS-CoV-2 vaccination. A diverse group with a range of ages, genders, and comorbidity statuses was represented by the total of 655 participants. This is advantageous, especially when researching immune responses in various populations. The kinetics of immune responses following SARS-CoV-2 vaccination were demonstrated by the longitudinal design, which also made it possible to assess immune responses in terms of their amplitude and persistence.

Assessment of cellular immune response

The cellular immune response to the virus was assessed using the activation-induced marker (AIM) assay, a highly sensitive and specific technique for identifying antigen-specific T cells

without the requirement to quantify cytokine production. PBMCs were separated from participant blood samples and activated with SARS-CoV-2 viral peptides produced from spike proteins. The antigen-specific CD4+ and CD8+ T cells were then identified using the expression of activation markers such as CD69, CD137, and OX40. It is the best way to measure the cellular immune response to the vaccine.

The production of cytokines such as interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-α) has been measured using similar immunological techniques using enzyme-linked immunospot (ELISpot) assays and multiparametric flow cytometry to expand the results obtained with the AIM-based approaches. Additionally, cytotoxic effects have been studied using markers like granzyme B and perforin, which measure CD8+ cells' capacity to lyse cells.

Assessment of humoral immune responses

Humoral immunity can also be measured by serological testing for SARS-CoV-2-specific antibodies. The number of antibodies against the virus, specifically the spike protein, is measured by analyzing blood samples. The degree of neutralising power of the vaccine is measured by antibody levels. Understanding cellular and humoral immunity is necessary for a deeper understanding of adaptive immunity.

Data collection and follow-up

The subjects were monitored over time following the immunization to assess the development of the immune response. This allowed for the identification of trends in the data, such as the peak and decrease of the immunological response. Comparisons over time and between various subject categories were nevertheless feasible despite the limitation that some of the individuals did not have baseline data.

Statistical Analysis

To determine the factors affecting the immune response, multivariable logistic regression analysis was used. This approach helps assess the independent link between the predictor variables, such as age, sex, and the comorbidity index, while controlling for confounding variables. Because the results are not impacted by bias and each variable's distinct contribution can be assessed, this approach is seen as more reliable. By assessing the statistical significance using the p-value and confidence interval, the results' dependability was guaranteed.

Results

The results also offer strong evidence that vaccine-induced T cell immunity is significantly influenced by age. It has been observed that elderly people, particularly those aged 75 and above, have much lower frequencies and functional capacity of CD4+ and CD8+ T cell responses to the spike protein antigen. This has also been accompanied by a decline in serological responses, suggesting a general weakening of adaptive immunity. These findings are consistent with the notion of immunosenescence, which is characterized by decreased naïve

T cell production, limited T cell receptor variety, and diminished effector function (Crooke et al., 2019; Sette & Crotty, 2021). The findings of Dietz et al. (2023) further support the notion that age is an independent predictor of decreased immune responses to vaccination, both at the cellular and humoral levels.

Comorbidities also had an impact on the age-related reduction in immune response. A higher chance of being categorized as "cellular hypo-responders," which are characterized by reduced T cell activation, proliferation, and cytokine production, was linked to higher comorbidity indices. Diabetes, cardiovascular disease, and chronic respiratory disorders all contribute to low-grade inflammation that lasts and results in immunological dysregulation, or "inflammaging," which disrupts regular immune signalling pathways (Franceschi et al., 2018). Consequently, lower cellular and humoral immune responses were observed to be associated with the cohort's higher comorbidity index.

Longitudinal research also shows how immunization alters the immune response. T cell proliferation, contraction, and stability after immunization show how the cellular response is dynamic. Booster shots and repeated vaccinations strengthen the immune response. Comorbid and elderly patients, however, experience relatively less improvement. Nonetheless, the boosters enhance T cell and antibody function, indicating a partial immune response recovery (Painter et al., 2021; Goel et al., 2022).

The integration of humoral and cellular immune responses highlights the multifactorial role of protective immunity against SARS-CoV-2. Some individuals with low antibody responses demonstrated strong T cell responses, suggesting that cellular responses compensate for the decline in humoral responses and play an important role in preventing severe outcomes from the virus (Sallusto et al., 2022). Additionally, the immune responses varied with age, with younger individuals and children displaying more diverse T cell responses, including cytokine secretion and cytotoxic activity (Grifoni et al., 2020).

Table 1: Impact of Age on Vaccine-Induced Immune Responses

Parameter	**Younger Individuals**	**Older Individuals (≥75 years)**
CD4+ T cell response	Robust activation	Reduced activation
CD8+ T cell response	cytotoxic activity	Decreased cytotoxic function
Antibody titers	High	Reduced
Immune memory formation	Efficient	Impaired
Overall adaptive immunity	Strong	Weakened (immunosenescence)

Table 2: Influence of Comorbidities on Immune Responses

Parameter	**Low Comorbidity Burden**	**High Comorbidity Burden**
T cell activation	Normal	Impaired
Cytokine production (IFN-γ, IL-2)	Adequate	Reduced
Inflammatory status	Controlled	Chronic low-grade inflammation
Vaccine responsiveness	Optimal	Reduced (“hypo-responders”)
Immune regulation	Balanced	Dysregulated

Table 3: Effect of Booster Vaccination on Immune Responses

Parameter	**Pre-Booster**	**Post-Booster**
CD4+ and CD8+ T cell response	Moderate / Declining	Enhanced
Antibody titers	Waning	Increased
Immune protection	Partial	Improved
Response in elderly/comorbid	Suboptimal	Partially restored

These structured findings reinforce the concept that both intrinsic factors (such as age) and extrinsic clinical conditions (such as comorbidities) significantly shape vaccine-induced immune responses, highlighting the importance of tailored immunisation strategies.

Discussion

The results of these studies, taken together, underscore the importance of T cell immunity in vaccine-induced protection against SARS-CoV-2. The reduction in immune responses in elderly individuals can be accounted for by immunosenescence, which affects the development of T cell immunity. This has serious implications for vaccine-induced protection, as a decrease in T cell responses may impair the ability to effectively counter the infection and its severity.

Because the comorbidities cause additional immune dysfunction, the situation becomes more complicated. Chronic inflammation is known to be brought on by diabetes and heart conditions,

which can hinder the body's ability to initiate T cell responses. Comorbidity indices are a useful foundation for predicting vaccine response in these kinds of investigations.

The significance of assessing both humoral and cellular immunity is another important realization. The actual level of immune protection may be underestimated by conventional evaluations that just look at antibody levels. Long-term immunity is greatly aided by T cell responses, which may offer defense even in the event that antibody levels decline. This is especially important when it comes to developing variations, where T cell recognition is largely unaffected but antibody escape may happen.

Despite these advancements, several limitations still exist. There may be residual confounding because many research, like Dietz et al. (2023), are observational in nature. Furthermore, because there is no clear correlation between immunological markers and clinical outcomes such breakthrough infections, it is challenging to fully assess the protective significance of reported immune responses. Because study populations and methods vary, it is often challenging to extrapolate findings to other demographic groups.

Conclusion

In conclusion, the protective advantages of SARS-CoV-2 vaccines are mostly dependent on T-cell-mediated immunity. Age and comorbidities have an impact on the quantity and quality of different types of immunity. Older people and those with comorbidities have lower immunity than younger people and those without comorbidities. Understanding these vaccine-induced protective benefits requires measuring humoral and cellular immunity.

These findings emphasize the necessity of particular vaccination tactics, such as boosters and/or alternative vaccinations, to improve immunity in these vulnerable populations. Future studies should aim to establish clear connections between the immune response and clinical protection. Additionally, they must to try to explain how immunity might be strengthened in these high-risk populations. Optimizing vaccination efforts to limit COVID-19 infection will require a deeper understanding of T cell immunity.

These results highlight the need for specific vaccination strategies, including boosters and/or alternate immunizations, to strengthen immunity in these susceptible groups. Future studies should aim to establish clear connections between the immune response and clinical protection. They must also attempt to elucidate how immunity may be bolstered in these high-risk groups. A better understanding of T cell immunity will be necessary to maximize immunization efforts to reduce COVID-19 infection.

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