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Factors Influencing Humoral Immunity Post COVID-19 Vaccination in Georgia

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ABSTRACT

COVID-19 vaccines have reduced severe disease and mortality worldwide. However, humoral immunity wanes over time, particularly against symptomatic SARS-CoV-2 infection (Andrews et al., 2022; Feikin et al., 2022). Vaccine effectiveness (VE) against symptomatic infection declines from ~53% one month post-vaccination to 14% at six months, while protection against severe disease remains above 70% (Tartof et al., 2021; Lin et al., 2022). Hybrid immunity—vaccination with prior infection—provides stronger and more durable protection (Chemaitelly et al., 2023; Pilz et al., 2022). Demographic and clinical factors, including age, comorbidities, and immunosuppression, influence responses, while sex differences are minor (Goel et al., 2021; Griffin, 2023). Genetic factors, particularly Rhesus (Rh) status, may shape humoral responses (Alavi et al., 2023; Musa et al., 2023). In Georgia, plasma donor data confirmed vaccination, hybrid immunity, and Rh positivity as predictors of protective titers. These findings support universal vaccination, timely boosters, and targeted protection.

Keywords: COVID-19; vaccination; humoral immunity; hybrid immunity; Georgia

INTRODUCTION

The rapid development and deployment of COVID-19 vaccines marked one of the most significant achievements in modern public health. Since early 2021, billions of doses have been administered worldwide, preventing millions of hospitalizations and deaths (World Health Organization, 2022). Yet despite their success, variability in immune responses soon became evident. Breakthrough infections, particularly during the Delta and Omicron waves, highlighted both waning immunity and viral immune escape (Pouwels et al., 2021).

Humoral immunity, mediated primarily through neutralizing antibodies, plays a central role in preventing infection. However, the magnitude and durability of antibody responses differ widely across individuals. Several domains contribute to this variability:

- **Temporal dynamics** – antibody titers peak after vaccination and subsequently decline (Andrews et al., 2022; Feikin et al., 2022).
- **Infection history** – hybrid immunity, combining prior infection with vaccination, offers broader and more durable protection (Chemaitelly et al., 2023; Pilz et al., 2022).
- **Demographic and clinical factors** – age, comorbidities, and immunosuppression can weaken immune responses (Goel et al., 2021; Griffin, 2023).
- **Genetic influences** – blood group and Rh factor may modulate antibody responses (Alavi et al., 2023; Musa et al., 2023).

Georgia provides a valuable case study. The country experienced moderate vaccine uptake alongside high exposure to natural infection. This environment allowed researchers to explore determinants of humoral immunity in a mixed-immunity setting. Data from 175 plasma donors provide unique insights into how global findings translate to local populations.

TEMPORAL DYNAMICS OF ANTIBODY RESPONSE

Waning of antibody levels

After vaccination, antibody titers rise rapidly, reaching their peak within a few weeks. However, these levels decline steadily thereafter. Andrews et al. (2022) reported that vaccine effectiveness (VE) against symptomatic infection with the Pfizer-BioNTech vaccine dropped from ~53% one month after the second dose to ~14% at six months. Similarly, Feikin et al. (2022), in a meta-analysis involving more than 25 million individuals, confirmed that waning immunity was consistent across both mRNA and adenoviral vector vaccines.

Protection against severe disease

Despite the decline in protection against infection, defense against hospitalization and death remains comparatively robust. Tartof et al. (2021) found that VE against hospitalization remained above 70% up to six months post-vaccination. Lin et al. (2022) demonstrated similar durability across different vaccine platforms. This sustained protection is attributed largely to cellular immunity, including memory B cells and T cells, which continue to provide defense even as antibody levels fall (Goel et al., 2021; Khoury et al., 2021).

Variant impact

The emergence of new variants has accelerated immune escape. Pouwels et al. (2021) showed that Omicron reduced VE more rapidly than Delta, due to extensive mutations in the spike protein. Consequently, VE against symptomatic Omicron infection was significantly lower than against earlier variants, with declines occurring within weeks rather than months.

Booster effects

Booster doses have proven effective in restoring protection, at least temporarily. Feikin et al. (2022) reported that VE against symptomatic infection increased to about 60% one month after a booster dose, though this protection declined to ~20% within 6–9 months. Variant-adapted boosters may provide improved durability and coverage against immune escape, and their periodic use could become necessary during future waves (Chemaitelly et al., 2023).

HYBRID IMMUNITY

Hybrid immunity—generated when vaccination is combined with prior SARS-CoV-2 infection—consistently provides stronger and more durable protection than either vaccination or infection alone.

Magnitude and durability

Chemaitelly et al. (2023), in a systematic review and meta-regression of 26 studies covering over eight million individuals, found that hybrid immunity maintained ≥95% protection against severe disease for up to 11 months after primary vaccination and ~95% at six months following a booster. Pilz et al. (2022) similarly reported that reinfection rates were lowest among hybrid immunity groups, even during the circulation of immune-evasive variants such as Omicron.

Immunological mechanisms

From an immunological perspective, the enhanced protection of hybrid immunity arises from complementary processes. Natural infection exposes the immune system to multiple viral proteins, broadening the antibody repertoire. Vaccination, on the other hand, focuses immune responses on the spike protein, encouraging affinity maturation and high-titer neutralization. Together, these exposures stimulate more robust memory B cell pools and polyfunctional T cell responses, leading to durable and broad-spectrum protection (Harrison et al., 2023).

Georgian evidence

In Georgia, plasma donor data confirmed the global pattern. Of individuals with hybrid immunity, 92.5% achieved protective antibody titers (≥1000 BAU/mL). This was significantly higher than the 77.8% of vaccinated-only participants and the 24.3% of infection-only individuals ($p < 0.001$). These findings emphasize the critical role of vaccination even in populations with high natural infection exposure.

DEMOGRAPHIC AND CLINICAL DETERMINANTS

Age

Age is one of the strongest predictors of reduced vaccine responsiveness. Older adults often mount weaker and less durable antibody responses due to **immunosenescence**, a gradual decline in immune function characterized by reduced naïve T cell production, diminished B cell diversity, and impaired memory responses (Weinberger et al., 2008). Even after booster doses, elderly populations generally achieve lower peak titers than younger individuals (Griffin, 2023). This reduced responsiveness contributes to their heightened vulnerability during COVID-19 surges and underscores the importance of prioritizing timely booster campaigns for older age groups.

Sex

Sex-related differences in vaccine-induced immunity have been observed but are relatively modest. Females often produce slightly higher antibody titers following vaccination compared to males. This difference is thought to result from hormonal influences—estrogen enhances, while testosterone may suppress immune function—and the presence of immune-regulatory genes on the X chromosome (Goel et al., 2021). However, these differences are small in magnitude and do not warrant sex-specific vaccination recommendations.

Comorbidities

Pre-existing health conditions also affect humoral immunity. Chronic illnesses such as **diabetes, obesity, cardiovascular disease, and chronic kidney disease** have been associated with diminished antibody responses to COVID-19 vaccines. Lin et al. (2022) demonstrated that patients with these comorbidities not only generated lower titers but also exhibited faster waning. Such findings are consistent with the increased COVID-19 severity observed in these groups.

Immunosuppression

Immunocompromised individuals represent a special challenge. Transplant recipients, cancer patients undergoing chemotherapy, and those on long-term immunosuppressive therapy frequently fail to achieve protective titers even after multiple vaccine doses (Andrews et al., 2022). These patients often require **additional booster doses**, heterologous vaccination strategies, or passive immunization (e.g., monoclonal antibodies) to maintain protection.

GENETIC DETERMINANTS

ABO blood groups

The role of ABO blood groups in COVID-19 susceptibility and vaccine response has been debated. Some studies suggest that individuals with **blood group O** have reduced risk of infection, while those with **group A** may face higher susceptibility (Liu et al., 2023; Al-Madani et al., 2023). However, these associations are inconsistent across populations, and evidence for an effect on vaccine-induced antibody responses is weak. Alavi et al. (2023) reported minor vaccine-specific differences: recipients of the AstraZeneca vaccine with blood type A displayed higher antibody rises, whereas blood type O was linked to more persistent responses in Sinopharm recipients.

Rhesus (Rh) factor

Evidence for the **Rh factor** is stronger. Alavi et al. (2023) observed significantly higher antibody responses in Rh-positive individuals across vaccine types. Musa et al. (2023) further reported that Rh-negative status was associated with higher mortality risk in COVID-19 patients. The mechanisms remain under investigation but may involve glycan-mediated immune modulation or differences in immune complex clearance.

Other genetic influences

Beyond ABO and Rh, emerging research points to broader **immunogenetic determinants**. The COVID-19 Host Genetics Initiative (2021) identified multiple genetic loci linked to COVID-19 severity, including variants in immune regulatory genes, interferon pathways, and HLA polymorphisms. These findings highlight that host genetics play an important role not only in susceptibility to severe infection but also potentially in shaping vaccine responsiveness. However, such associations remain preliminary and require confirmation in large, multi-ethnic cohorts.

GEORGIAN COHORT FINDINGS

A study of **175 plasma donors in Georgia (2022–2023)** provided regional evidence that aligns with and extends global findings.

- **Vaccination effect**: 81.9% of vaccinated individuals achieved protective antibody titers (≥1000 BAU/mL), compared with only 21.0% of unvaccinated donors (OR = 16.88, 95% CI: 8.54–33.37, $p < 0.001$).
- **Hybrid immunity**: 92.5% of participants with both prior infection and vaccination achieved protective titers, compared to 77.8% of vaccinated-only and 24.3% of infection-only groups (OR = 57.58 vs neither, $p < 0.001$).

- **Rh factor**: Rh-positive individuals showed significantly stronger protective responses than Rh-negative (57.7% vs 30.8%, p = 0.011).
- **ABO groups**: No statistically significant association was observed (p = 0.374).

These results confirm that vaccination and hybrid immunity remain the strongest predictors of protection in the Georgian population, while Rh factor may represent a novel genetic determinant of humoral response.

TABLE 1. Determinants of humoral immune response: global evidence vs Georgian cohort

Determinant	Global Evidence (selected sources)	Georgian Evidence
Waning immunity	VE falls from ~53% at 1 month → ~14% at 6 months (Andrews; Feikin; Tartof; Lin)	Decline observed in plasma donor data
Hybrid immunity	≥95% protection up to 11 months (Chemaitelly; Pilz; Harrison)	92.5% vs 77.8% vaccinated only
Age/comorbidities	Older adults, diabetes, obesity reduce responses (Goel; Griffin)	Not directly assessed
Sex	Females slightly higher titers (Goel)	Not studied
ABO group	Mixed findings; weak associations (Liu; Al-Madani)	No association (p = 0.374)
Rh factor	Rh+ stronger antibody rise (Alavi; Musa)	Rh+ 57.7% vs Rh– 30.8% (p = 0.011)

PUBLIC HEALTH IMPLICATIONS

The convergence of global evidence with Georgian cohort findings highlights several key implications for public health policy and vaccination strategy.

Booster timing

Because vaccine-induced antibody levels wane rapidly, timely **booster administration** is essential. Data suggest boosters may be required every **4–6 months** during periods of high transmission to sustain adequate protection against symptomatic infection. This is especially critical for populations at higher risk of severe disease, including older adults and individuals with chronic conditions.

Universal vaccination

Hybrid immunity data confirm that **all individuals benefit from vaccination**, regardless of prior infection history. Relying solely on natural infection provides incomplete and short-lived immunity. Universal vaccination should therefore remain a cornerstone of pandemic control strategies, even in countries with widespread prior exposure.

Targeted strategies

Certain groups may require **tailored approaches**. Elderly individuals, immunocompromised patients, and Rh-negative populations are more likely to exhibit reduced humoral responses. Strategies for these groups may include additional booster doses, closer serological monitoring, or alternative preventive measures such as monoclonal antibody prophylaxis.

Variant readiness

The rapid emergence of immune-evasive variants such as Omicron underscores the need for **variant-adapted vaccines**. Incorporating dominant strain antigens into updated boosters could improve the breadth and durability of protection.

Global equity

Disparities in vaccine access remain significant. Many low- and middle-income countries continue to face barriers in securing adequate supplies of primary and booster doses. Global coordination is needed to ensure equitable distribution, preventing immunity gaps that could foster new variant emergence.

RESEARCH GAPS AND FUTURE DIRECTIONS

Despite significant advances in understanding vaccine-induced immunity, important gaps remain:

1. **Durability beyond 12 months**

   Most studies track antibody levels for up to a year, but longer-term data are scarce. Extended follow-up is needed to determine whether hybrid immunity or repeated boosters provide lasting protection across different populations.

2. **Cellular immunity**
   Antibody titers are only one correlate of protection. More research is required on **T cell–mediated immunity** and memory B cell function, which likely underpin durable defense against severe disease even as antibody levels decline (Khoury et al., 2021).
3. **Host genetics**
   While ABO and Rh have received attention, broader genetic studies are needed. Large, multi-ethnic cohorts with **genome-wide association studies** (GWAS) could clarify the roles of HLA polymorphisms, Fc receptor variants, and innate immunity genes in shaping vaccine response.
4. **Variant-adapted vaccines**
   As new variants emerge, there is a need to evaluate the **efficacy and durability** of updated formulations. Research should assess whether variant-specific boosters provide broader and longer-lasting protection than existing platforms.
5. **Population-specific data**
   Regional cohorts, such as the Georgian study, are vital for contextualizing global findings. Local epidemiology, infection history, and vaccine use patterns can significantly influence immune outcomes, emphasizing the need for **country-level research** to inform national policy.

CONCLUSIONS

Humoral immune responses after COVID-19 vaccination are shaped by a combination of temporal dynamics, prior infection, demographic and clinical factors, and host genetics. Vaccination remains the strongest predictor of protective antibody titers, while hybrid immunity provides the most robust and durable protection. Age, comorbidities, and immunosuppression significantly reduce vaccine responses, and the Rhesus (Rh) factor emerges as a potential genetic determinant.

In Georgia, plasma donor data confirm these trends: vaccination and hybrid immunity were the most powerful predictors of protective titers, while Rh positivity was associated with stronger responses. These findings highlight the importance of **universal vaccination**, **timely booster campaigns**, and **targeted monitoring** of vulnerable groups. Integrating both global and local evidence will be essential for shaping effective, evidence-based immunization policies in the years ahead.

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