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Coronavirus Pandemic

Molecular mechanisms responsible for SARS-CoV-2 antibody waning and vaccine escape in Omicron sublineages BA.4 and BA.5

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Abstract

Mutations in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome continue to threaten the global landscape of the coronavirus disease 2019 (COVID-19) pandemic. The Omicron variant (B.1.1.529) rapidly displaced previous 'variants of concern' (VoC) in 2021 due to its high rate of transmissibility and multitude of mutations. This global influx of infections saturated healthcare systems, overwhelmed testing capacity and case reporting, and increased the COVID-19 death toll. Global health leaders are now being faced with the most transmissible COVID-19 variants yet, the Omicron sublineages BA.4 and BA.5, which contain additional spike protein (S) mutations from previous Omicron and VoC serotypes. With universally observed antibody waning, increasing vaccine-variant mismatch, and resuming international travel, the stage is set for unprecedented levels of breakthrough infections and superspreading events. In this paper, we raise awareness to these novel variants and provide context for the high likelihood of an upcoming wave of infection capable of inflicting significant disease burden on a global scale.

Key words: Vaccination fatigue; vaccine-variant mismatch; antibody escape; variants of concern (VoCs); breakthrough infection.

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Introduction

A common theme of the COVID-19 pandemic is the increasing incidence of "breakthrough infections". A breakthrough infection is defined as a fully vaccinated individual (that is, already having two or more doses of a reputable SARS-CoV-2 vaccine) contracting a SARS-CoV-2 infection [1]. Although messenger RNA (mRNA)-based vaccines offer vaccinees protection from severe disease, it currently remains to be elucidated whether long-term protection and recurrent vaccine doses are necessary for sustained protection from infection. Recently, the Omicron (B.1.1.529) SARS-CoV-2 variant and its sublineages (BA.1, BA.2, BA.3, BA.4, and BA.5) have rapidly spread around the globe, becoming the dominant variant in many countries ahead of variants such as Delta (B.1617.2) and Alpha (B.1.1.7). The initial Omicron variant (BA.1) spike protein (S) contains 30 amino acid (aa) substitutions, 6 aa deletions, and 3 aa insertions when compared to ancestral strains [2]. These extensive S mutations observed in Omicron are, in-part, responsible for the variants' increased transmissibility, where active interference with the angiotensin converting enzyme 2 (ACE2) surface and changes in the N protein N-terminal domain (NTD) cause reduced neutralization capacity from vaccine induced and convalescent serum. This results in increased levels of breakthrough infections when coupled with waning of vaccine induced antibodies and increasing levels of vaccine-variant mismatch, where novel variants (particularly BA.4/.5) become structurally and functionally dissimilar to early iterations of COVID-19 vaccines, such as Comirnaty® (BNT162b2, Pfizer-BioNTech) and Spikevax® (mRNA1273, Moderna). Although infections caused by the Omicron variant are generally regarded as being less severe, the rapid influx of cases and high transmissibility rate has led to many deaths and severe cases are still frequently reported [3,4]. In response, this contribution aims to provide early evidence that public health will encounter subsequent,

Omicron sublineage driven waves of infection necessitating further global pandemic mitigation and vaccination efforts.

BA.2, BA.4, and BA.5

The emergence of the Omicron SARS-CoV-2 variant has led to unprecedented case numbers and deaths around the globe. The transmissibility and virulence of Omicron and its sublineages is partially explained by the myriad of genetic and protein level mutations (Table 1) compared to other World Health Organization (WHO) recognized VoCs. Interestingly, Omicron BA.4 and BA.5 sublineages are both derived from the B.1.1.529 Omicron clade and each shares the same mutation profile in the S protein [5].

These morphological changes, coupled with waning vaccine coverage and increased vaccine-variant mismatch, resulted in the rapid spread and replacement of Delta (B.1.617.2) as the globally dominating variant. Recent findings suggest that the subsequent emergence of the highly transmissible Omicron BA.2 sublineage has displaced the original Omicron variant to become the most prominent strain [6]. Importantly, two studies have now found that BA.2.12.1 and BA.4/BA.5 exhibit stronger neutralization evasion than BA.2 against sera from individuals with three mRNA vaccine doses, and that these viruses can effectively evade neutralization by antibodies produced by post-vaccination BA.1 infections [2,7]. Although breakthrough infection with Omicron BA.1 cases have been high in fully vaccinated individuals (2-3 doses), the antibodies produced by these infections demonstrated strong neutralizing activity against Omicron BA.1, BA.2, and previous SARS-CoV-2 VoCs [8,9]. However, the same level of neutralization was not observed for novel Omicron sublineages BA.4 and BA.5. With these data, it is evident that further studies are needed to delineate whether an individual can undergo multiple, distinct Omicron sublineage infections in a short time, and the extent to which BA.1-tailored mRNA vaccines, such as those from Pfizer-BioNTech, are able to stave off infection and severe disease resulting from exposure to BA.4 and BA.5. These results also suggest that as BA.4 and BA.5 begin to displace previous Omicron variants, future pandemic waves are inevitable and may possess similar healthcare-saturating characteristics to the original BA.1 Omicron variant. Interestingly, early (pre-print) data have found that BA.4 and BA.5 may also possess increased infiltration capacity in human alveolar epithelial cells, potentially causing more severe disease than previous Omicron waves [10]. Taken together, it is important to critically evaluate current levels of preparedness for emerging, virulent SARS-CoV-2 variants and how, as a global community, we can begin to address deficiencies in current vaccine rollout and practices. Future waves will necessitate additional vaccine doses to protect those at greatest risk, such as the immunocompromised, elderly, and those with underlying health conditions. This raises the concern of 'vaccination fatigue' and the global population's attitude towards successive rounds of vaccine boosting.

Vaccination Fatigue

As rapid SARS-CoV-2 viral evolution drives considerable protein-level and genetic mutations in the S and receptor binding domain (RBD) regions, it becomes increasingly likely that additional vaccines will need to be administered and re-developed to address changes being observed in emerging variants. For much of the developed world, individuals have had at least two doses of mRNA vaccines, with many at-risk groups having received third and fourth booster doses to combat waning, vaccine induced, free-circulating neutralizing antibody levels. As the stringency of public health measures (such as mask wearing, social distancing, hygiene, gathering limitations, etc.) have been reduced or removed altogether in many countries, confusion and apprehension have begun to polarize the vaccinated population. Many people are becoming

Table 1. SARS-CoV-2 variants and their spike protein (S) mutations compared to the ancestral Wuhan strain.

SARS-CoV-2 Variant	Genetic Mutation	Region on Spike Protein
Alpha (B.1.1.7)	E484K, N501Y, D614G	RBD
Beta (B.1.351)	E484K, N501Y, D614G, K417N	RBD
Gamma (P.1)	E484K, N501Y, D614G, K417T, H655Y	RBD
Delta (B.1617.2)	D614G, L452R, T478K, P681R	RBD, NTD, and furin-cleavage site on the S2 region
Omicron (B.1.1.529)	N501Y, G339D, S371L, S373P, S375F, N440K, G446S, T478K, G496S, Q498R, K417N, S477N, E484A, Q493R, Y505H	RBD
BA.2 (B.1.1.529.2)	T191, A27S, V213G, S371F, T376A, D405N, R408S	NTD and RBD
†BA.4/BA.5 (B.1.1.529.4/5)	L452R, F486V, R493Q, 69-70△	NTD and RBD

RBD: Receptor binding domain; NTD: N-terminal domain; †: coupled accounting for identical spike protein genetic changes.

weary and frustrated by the rise of breakthrough infections and the notion that there is no foreseeable 'end in sight' for COVID-19 vaccinations as the virus continues to mutate and evade neutralizing antibodies. This apathy and indifference is being referred to as 'vaccination fatigue', which is the inertia or inaction of a person towards vaccine information or instruction due to both burden and burnout [11]. One study from Su *et al*. (2022) found that 'vaccine fatigue' has been observed in the public, children's parents, policymakers, and healthcare professionals and is predominantly driven by the vaccination frequency being recommended by public health authorities, vaccine side effects, disease severity, and a lack of trust in the government and media [11].

To address vaccine escape and the everchanging SARS-CoV-2 landscape, a shift in vaccination efforts is necessary to overcome breakthrough infections and combat the public's dwindling faith in the effectiveness of current vaccine options. Potential solutions to vaccine waning include (but are not limited to): i) further investigation into second generation, multivalent vaccines, ii) the humoral IgA mucosal response, and iii) development beyond S-targeting vaccines towards broad stimulation and priming of adaptive T- and B-cell mediated memory responses. A multivalent COVID-19 vaccine may address deficiencies in existing mRNA-based vaccines, such as the existing reliance on multiple doses and the lack of infection [1]. Multivalent vaccines rely on incorporating SARS-CoV-2 S epitopes from multiple variants, rather than just a single variant. This would augment current mRNA vaccines by stimulating a broader antibody response and more extensive levels of protection. Furthermore, the time lag between the development of an mRNA vaccine against an emerging variant is such that many individuals may be experiencing infection caused by a more recent variant with a different antigenic profile compared to that of the original vaccine [12]. This delayed reactionary response determines that, regardless of the speed of production, vaccine coverage will lag behind emerging VoCs indefinitely. Additional evidence suggests that changing the route of vaccination may also be advantageous. For example, for full protection against viral infection, sterilizing immunity at the site point of infection may be required. For COVID-19, this is neutralizing antibodies at mucosal sites in the nose, throat, and upper respiratory tract achieved by intranasal (IN) vaccines [13]. Early data indicate that a heterologous vaccination with an mRNA intramuscular (IM) vaccine prime coupled with an IN boost could result in broader protection, both systemically and at the infection site [1,14].

Concluding Remarks

Overall, these data highlight the importance of continued SARS-CoV-2 vaccine development in the context of novel, emerging virus variants. The additional S mutations observed in Omicron sublineage variants BA.4 and BA.5 render antibodies produced by mRNA vaccination and previous Omicron BA.1 infection ineffective at neutralizing circulating virus. Furthermore, given current trends in Omicron-related SARS-CoV-2 outbreaks, it is likely that an additional BA.4/BA.5 driven wave will be experienced globally in the fall of 2022. This is over particular concern as travel resumes to pre-pandemic levels.

As the population continues to endure successive waves of infection and ever shifting pandemic policies, it is likely that vaccination fatigue and reduced 'buy-in' will be felt around the world. This presents a unique situation for governing health authorities, who will need to potentially manage a more severe rapidly spreading variant, which is capable of re-infecting individuals with previous Omicron BA.1 infections. This letter should serve both as a "warning flare" for what's to come, as well as to provide framework for decreasing the burden of subsequent waves of COVID-19.

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