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Duelling Variants: Omicron BA.1 And B.A.2- A Fight to The Finish?

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1. Abstract

Since the emergence of SARS Coronavirus 2 (SARS-CoV-2, in 2019, it has caused over 300 million cases and 5.5 million deaths [1]. SARS-CoV-2is an enveloped, positive-sense, single-stranded RNA virus having approximately 30,000 nucleotides. The initial virus spread globally was characterized by a D614G change in the spike (S) protein [2] Within a year, multiple variants emerged with several mutations in the spike protein across various countries- the United Kingdom(Alpha), South Africa(Beta), and Brazil(Gamma). In April 2021, the Delta variant emerged initially in India and rapidly replaced Alpha globally over the next few months [3].

SARS-CoV-2 belongs to:

- Order Nidovirales,
- Family Coronaviridae,
- Subfamily Orthocoronavirinae,
- Genus Betacoronavirus
- Subgenus Sarbecovirus,
- Species Severe acute respiratory syndrome-related coronavirus
- Individuum SARS-CoV-2 with the addition of the strain/ sequence, e.g., SARS-CoV-2 Wuhan-Hu-1 as the reference strain [4].

New and Emerging variants are termed Variants of Concern (VOC) by WHO based on the below factors:

a) Depict a major change in epidemiology and/or clinical presentation

b) Have increased virulence

c) Show increased transmissibility

d) Exhibit decreased effectiveness of public health and social measures or available diagnostics, vaccines or therapeutics [5]. Omicron (Pango lineage B.1.1.529) emerged as VOC on November 19, 2021, in Botswana and South Africa and has been rapidly disseminated globally and now dominates in many countries. Its BA.1 subvariant (or Nextstrain clade 21K) has dominated most parts of the world. The number of cases attributable to BA.1's sister subvariant, BA.2, has risen lately. Highly contagious BA.2 subvariant (or Nextstrain clade 21L) is now dominant in many countries and is on the rise globally-after squeezing out other Omicron subvariants featuring different mutations, including the original lineage, as well as variants, namely BA.1, BA.1.1 and BA.3. Omicron carries more than 30 mutations and deletions in the spike gene than the original Wuhan strain and is associated with increased transmissibility and immune escape [6]. Studies indicate that the Omicron variant results in less severe disease outcomes than Delta [7].

BA.2 varies from BA.1 in its genetic sequence, including some amino acid variations in the spike protein and other proteins. Recent studies have indicated that BA.2 has a growth advantage over BA.1, i.e. increased transmissibility. This variation in transmissibility appears to be much lesser than, for example, the difference between BA.1 and Delta. BA.1 and BA.2 lineages were found to have 51 mutations dispersed throughout the genome, 32 of which are common to both lineages, whereas each lineage has 19 signature mutations. Of the 32 common mutations, 21 are in the S glycoprotein and the remaining 11 in the other coding regions-ORF1ab, E, M, and N. In BA.1, 19 unique mutations contain 13 in the

S glycoprotein region; correspondingly, BA.2 has 7 in the S glycoprotein region. The difference between Omicron BA.1 and BA.2 in the spike protein is larger than the variation between the Wuhan and the Alpha variant [8]. The S glycoprotein facilitates virus attachment to the Angiotensin Converting Enzyme(ACE2) receptor, membrane fusion, and entry into the host cell, and also acts as a prime target for neutralizing antibodies stimulated by the host immune response [9]. Mutations in the S glycoprotein of BA.1 and BA.2 raise a concern about whether these lineages have increased transmissibility, immune escape potential, and virulence compared to other prevalent SARS-CoV-2 strains especially Delta.

Analyzing the current situation with the global upsurge in omicron cases, a couple of critical questions arise:

a) Whether reinfection with omicron BA.2 variant is occurring following BA.1?

b) And if yes, what is the severity?.

Infection, more than once, by subvariants in the Omicron family does seem possible but appears rare, scientists in Denmark found in a recent real-world study — offering reassurance that countries won't experience another sudden surge of infections. A study from Denmark also stated that among the cases in which individuals first became infected by BA.1 and then by BA.2, most of the infected were unvaccinated and young, and most exhibited mild symptoms. The variance between the severity during their first and second infection was negligible. No infected individuals exhibited serious illness, and encouragingly-none required hospital admission. The study shows that infection with two different Omicron subtypes is possible, and reinfections have mainly affected younger unvaccinated individuals with mild symptoms [10]. Real-world data on clinical severity from the U.K., South Africa, and Denmark, where immunity (from vaccination or natural infection) is high, shows no reported difference in seriousness between BA.2 and BA.1. Reinfections were characterized by mild symptoms compared to the initial infection and did lead to neither hospitalization nor death. It is, however, striking that mainly children and adolescents become reinfected since children, to a higher degree than adults, develop a sustained cross-reactive immunity [11]. While BA.1 is deficient in one of the three target genes utilized in widespread SARS-CoV-2 testing, making it easily detectable - a process known as S-gene target failure due to multiple deletions in the NTD of S glycoprotein. BA.2 can't be found in the same way as it lacks deletions in the NTD.

Table 1: Shows various common and unique mutations of S protein [9].

Common mutations of BA.1 and BA.2 lineages (n=32), 21 in spike protein	Unique mutations of BA.1 lineage(n=19),13 in spike protein	Unique mutations of BA.2 lineage(n=19),7 in spike protein
S glycoprotein: G142D, G339D,S373P, S375F, K417N, N440K,S477N, T478K, E484A, Q493R,0498R. N501Y, Y505H,D614G, H655Y, N679K,P681H, N764K, D796Y,Q954H, N969K	S glycoprotein: A67V, HV69del,1951,VYY143del, N211del,L2121, 215EPEins, S371L, G446S,G496S, T547K, N856K, L981F	S glycoprotein: T191, LPPA24S,V213G, S371F, T376A, D405N,R408S

2. Conclusion

The emergence and rapid spread of the heavily mutated Omicron BA.1 and BA.2 variants suggest that population immunity exerts strong selective pressure on SARS-CoV-2, favouring the emergence of new antigenic variants. As the number of SARS-CoV-2 variants increases, it will become increasingly important to visualize and understand the antigenic relationships between variants [12]. While the two Omicron variants are antigenically distinct and need a different mode of detection, they have shown a remarkable similarity in their severity, symptoms and spread.

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