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Duelling Variants: Omicron BA.1 and BA.2 - A Fight to the Finish?

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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-2 is an envelope, positive sense, single stranded RNA virus having approximately 30, 000 nucleotides. The initial virus that spread globally was characterized by a D614G change in the spike (S) protein.[2] Within an year multiple variants emerged with several mutations in the spike protein across multiple countries- 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 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 as Variants of Concern (VOC) by WHO based on 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, 2021in Botswana and South Africa and has been rapidly disseminated globally and now dominates in many countries. Its BA.1 sub variant (or Nextstrain clade 21K) has dominated in most parts of the world. The proportion of cases attributable to BA.1's sister sub variant, BA.2, has begun to rise lately. Highly-contagious BA.2 sub variant (or Nextstrain clade 21L) is now dominant in many countries and is on the rise globally - after squeezing out other Omicron sub variants 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 compared to 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. In 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]

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

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] Presence of mutations in the S glycoprotein of BA.1 and BA.2, raise concern whether these lineages have increased transmissibility, immune escape potential, and virulence in comparison with other prevalent SARS-CoV-2 strains especially Delta.

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

a) Whether re-infection with omicron BA.2 variant is occurring following BA.1?
b) And if yes, what is the severity?

Infection, more than once, by sub variants 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. Study from Denmark also stated that among the cases in which individual first became infected by BA.1 and then by BA.2 the majority 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 admission to hospital. In summary, the study shows that infection with two different Omicron subtypes is possible and re-infections have mainly affected younger unvaccinated individuals with mild symptoms. Real-world data on clinical severity from U.K., South Africa, and Denmark, where immunity (from vaccination or natural infection) is high, shows no reported difference in severity between BA.2 and BA.1.

Re-infections were characterized by mild symptoms comparable to the initial infection and did lead to neither hospitalization nor death. It is, however, striking that mainly children and adolescents become re-infected, since children to a higher degree than adults develop a sustained cross-reactive immunity.[10]

While BA.1 lacks one of the three target genes used in widespread SARS-CoV-2 testing, making it easy to spot - a process known as S-gene target failure due to multiple deletions in the NTD of S glycoprotein. BA.2 can't be detected the same way as it lacks deletions in the NTD.

Conclusion

The emergence and rapid spread of the heavily mutated Omicron BA.1 and BA.2 variants suggests that population immunity is exerting 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. While the two Omicron variants are antigenically distinct and need a different mode of detection, however they have shown a remarkable similarity in their severity, symptoms and spread.

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