In brief

Emerging variants

13 May 2022

Summary

- The World Health Organization is monitoring BA.1, BA.2, BA.3, BA.4, BA.5 and descendent lineages and BA.1/BA.2 circulating recombinant forms such as XE under Omicron; however, the World Health Organization advises that public health authorities should monitor descendant lineages as distinct lineages.1
- Variants under monitoring listed by the World Health Organization include B.1.640 and XD recombinant (Delta AY.4 and Omicron BA.1).1
- Three Omicron sublineages BA.4, BA.5 and BA.2.12.1 have acquired additional mutations that may impact their characteristics (BA.4 and BA.5 have the del69/70, L452R and F486V mutations; BA.2.12.1 has the L452Q and S704L mutations).2

BA.2.12.1

- In the week ending 30 April 2022, BA.2.12.1 made up 36.5% of all newly sequenced positive COVID-19 tests in the United States.[3]
- Preliminary data suggests that BA.2.12.1 exhibits increased ACE2-binding affinities compared to BA.1.[4]
- Early data suggests use of pOGTF as a proxy for BA.2.12.1 provides faster tracking than whole genome sequencing.[5]
- Early reports of a growth advantage for BA.2.12 over BA.2.[6]
- There are evaluations on the sensitivity of BA.2.12.1 to eight therapeutic monoclonal antibodies. Findings from two studies suggest several antibodies are less effective against BA.2.12.1.[7, 8]

BA.4 and BA.5

- In a risk assessment published by the United Kingdom Health Security Agency on 28 April 2022 on BA.4 and BA.5 sublineages there was:
    - evidence of an overall growth advantage (red status with low level confidence) compared to BA.2 in the context of South Africa
    - insufficient data to report on transmissibility
    - evidence of some antigenic change (red status with moderate level confidence) compared to BA.2 based on structural modelling and pseudovirus neutralisation data
    - insufficient data to report on infection severity.[9]
- The European Centre for Disease Prevention and Control reported no current evidence for impact on transmissibility or on severity for BA.4 and BA.5 on 5 May 2022. However, early data suggests increased impact on immunity.
- Mutation profiles:

  - BA.4 shares all mutations and deletions with the BA.2 lineage except the following:
    - S: 69/70 deletion, R408 (WT), L452R, F486V, Q493 (WT)
    - ORF 7b: L11F
    - N: P151S
    - synonymous SNP G12160A.
  - BA.5 shares all mutations and deletions with the BA.2 lineage except the following:
    - S: 69/70 deletion, R408 (WT), L452R, F486V, Q493 (WT)
    - ORF6: D61 (wild type)
    - M: D3N
    - synonymous SNPs: G12160A, A27038G, and C27889T.

- Preliminary data suggests BA.4 and BA.5 sequences have the 69-70 deletion responsible for S gene target failure (SGTF).[2]
- Early reports suggest the observed escape of BA.4 and BA.5 from BA.1 elicited immunity is more moderate than the escape of BA.1 from previous immunity.[4, 10] One study showed that the BA.1 infection elicited neutralising capacity against BA.4 and BA.5 was five-fold higher in vaccinated individuals (Comirnaty and Johnson & Johnson) than unvaccinated individuals.[10]
- BA.4 and BA.5 have rapidly replaced BA.2, reaching more than 50% of sequenced cases in South Africa.[11] Estimated growth advantages for BA.4 and BA.5 are 0.08 and 0.12 per day respectively over BA.2 in South Africa.[11]
- According to the National Institute for Communicable Disease from South Africa, as of 4 May 2022, there was no indication that the BA.4 and BA.5 will increase the risk of developing severe disease in South Africa. However, the situation will continue to be monitored.[12]
- A preliminary comparative analysis and modelling study projected that the BA.4 and BA.5 are about 36% more infectious than BA.2 and will likely to become the new dominant variant.[13]
- Evaluations on the sensitivity of BA.2.12.1 and BA.4/5 to eight therapeutic monoclonal antibodies (bamlanivimab, bebtelovimab, casirivimab, cilgavimab, etesevimab, imdevimab, sotrovimab and tixagevimab) showed that bebtelovimab had two-fold more neutralising activity against BA.2 and other Omicron subvariants than against the parental virus (B.1.1). Sotrovimab had a 20-fold reduced neutralising activity against BA.2 than against the parental virus, however, it had more neutralising activity against BA.2.11 and BA.4/5 than against BA.2. Cilgavimab was active against BA.2, however, in comparison had 2-5-fold reduction in neutralising activity against BA.2.12.1 and 30-fold reduction against BA.4/5.[7]

Recombinant lineages

- There are reports of three recombinant lineages: XD, XE and XF.[14] The United Kingdom Health Security Agency identified two different combinations of Delta and BA.1 (XD and XF).[14]
- XD and XF are combinations of Delta AY.4 and BA.1. XD has the Omicron S gene incorporated into a Delta genome. XE is a combination of BA.1 and BA.2, with most of the genome including the S gene belonging to BA.2.[14]
- The XD recombinant is a variant under monitoring by the World Health Organisations and XE is monitored as Omicron.[15]

- It is estimated that XE has a growth rate 12.6% above that of BA.2.[16]
- There are reports that XF is no longer detected in the European Union and European Economic Area.[17]
- Early data suggests Delta-Omicron recombinant infections are rare and there is no evidence of increased transmissibility compared to other Omicron lineages.[18]
- Early reports suggest there is no current evidence that XD is associated with higher transmissibility or more severe outcomes.[19]

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