Summary

The emergence of the WHO designated "Omicron" lineages in November 2021 have pushed researchers and public health officials to design experimental assays to determine how to best respond to this new variant. Below we summarize experimental data relating to the BA.2 lineage of Omicron.

Omicron Lineages

5 Pango lineages fall under the “Omicron” designation (as of Feb 15, 2022):
- **B.1.1.529**: The parental lineage from which other sub-lineages evolved.
- **BA.1**: The most common form of “Omicron” at this time.
- **BA.1.1**: A sub-lineage of BA.1, containing the following “antibody escape” mutation in the spike protein: R346K.
- **BA.2**: A sister lineage that shares some mutations with BA.1, but also contains several unique mutations throughout its genome (See Fig.1).
- **BA.3**: Another sister lineage that shares some mutations with BA.1 and BA.2.

BA.2 Reference Genome

An early, complete genome assigned as BA.2: Australia/QLD2568/2021. OM371884 is an equivalent (100% sequence identity), publicly available genome.

Epidemiology

- The WHO’s latest weekly epidemiological report (Edition 78, 8 Feb 2022) has reported that BA.2 is now circulating in 69 countries globally.
- While total numbers of BA.2 remain small in the USA, proportions of BA.2 are on the rise, and the CDC has added the BA.2 lineage to its variant tracker.
- The Danish Statens Serum Institute’s latest report (Week 6, 2022) has also reported a possible sub-lineage of BA.2 containing the following mutation in ORF3a: H78Y, and which was responsible for 24% of cases.
- The UK’s Health Security Agency’s 36th Technical Briefing, also highlights an increasing proportion of BA.2 sequences.
- Recent statistical analysis from Yamasoba et al. estimated that the effective reproduction number of BA.2 was 1.4-fold higher than BA.1 (6).
- A hierarchical Bayesian multinomial logistic regression model calculated that BA.2 has a 8.9-fold higher fitness level than the original A lineage, the highest fitness of any lineage to date (8). BA.2 was found to be 1.3 fold more fit than BA.1, in agreement with numbers from Yamasoba et al.

Transmissibility

There is some early data that predicts that BA.2 may be somewhat more transmissible than BA.1. A study conducted by Denmark’s Statens Serum Institute on household transmission of BA.1 versus BA.2 found that BA.2 was “significantly” more transmissible than BA.1(1).

Independent research from the UKHSA also found that BA.2 had higher transmissibility than BA.1(2), with new data suggesting that “the average time from symptom onset of a primary case to symptom onset in their identified contacts (the mean serial interval) is around half a day shorter for BA.2 than BA.1”.

Data from the UKHSA note that ACE2 binding was higher for the BA.2 receptor binding domain compared to that of BA.1 (11).
**Immune Escape (Convalescent sera & Vaccines)**

**New data** indicates that despite significant differences between BA.1 and BA.2 in the spike receptor binding domain, lineages may behave similarly with respect to vaccine induced neutralizing antibodies (NAb). A study looking at the ability of sera from individuals who received 2 doses of the BNT162b2 mRNA vaccine, found that neutralizing antibody titers from to BA.2 were similar to those from BA.1 (3). A third boost further increased NAb levels. This study also showed that vaccinated individuals infected with BA.1 developed robust NAb titers to BA.2, indicating a significant level of cross-reactive immune protection.

A study by Yamasoba *et al.* confirmed BA.2’s resistance to neutralizing sera elicited either by mRNA-1273 and ChAdOx1 vaccines or by previous infection (6).

There is also evidence that at least some cross-protection against BA.2 is provided by previous infection with BA.1:
- Hamsters previously infected with BA.1 appeared to have cross protection against infection with the BA.2 variant, but not against Delta (11).
- Data from Stegger *et al.* in Denmark showed that while BA.2 reinfections can occur shortly after a BA.1 infection, they are generally rare and resulted in mild disease (12).
- A manuscript by Chemaitelly *et al.* also reported that previous BA.1 infection provided some but not complete protection against reinfection with BA.2 (14). More detailed data on the distinct differences between antigenic escape of the BA.1 versus the BA.2 variants was recently published in a paper by Mykytyn *et al.*, describing the use of an antigenic cartography to quantify and visualize antigenic differences using hamster sera obtained after primary infection (13).

**Immune Escape (Therapeutic Antibodies)**

A recent study has shown that BA.2 has significant ability to escape neutralization by 17 out of 19 monoclonal antibodies tested, including S309 (sotrovimab), one of the only effective and FDA approved mAb (4). Another study confirmed BA.2’s resistance to therapeutic mAbs including sotrovimab (6). Another study using a spike protein-pseudotyped lentivirus assay, demonstrated that BA.2 was not neutralized by any of the therapeutic monoclonal antibodies, including Sotrovimab and Evusheld mAbs (9).

However a press release from the FDA on Feb 11, 2022, authorized a new monoclonal antibody, bebtelovimab, that retains activity against BA.2.

**Pathogenicity data**

Preliminary data showed that BA.2 was both more replicative and more fusogenic (in a TMPRSS2-dependent fashion), in human nasal epithelial cells than BA.1 (6). *In vivo* data in hamsters also indicated that BA.2 may be more pathogenic than BA.1, with higher viral loads (~9-fold) found in the lungs for BA.2 than for BA.1 (6). Immunohistochemical assays showed that BA.2 was also found more frequently, in more distal areas of the lower respiratory tract, and caused more inflammation than BA.1, suggesting more efficient within host transmission.

More recent data reported by Imperial College UK noted that hamsters infected with BA.2 showed mild disease, similar to those infected with BA.1 (11). Human clinical data from S. Africa comparing disease severity of BA.2 to BA.1, found that severity of illness was comparable (10). Data from the UKHSA confirms that the risk of hospitalisation was not higher following a BA.2 infection than for BA.1 (11).
Diagnostic Tests & Amplicon Sequencing
- BA.2 does not have the S:69/70 deletion that causes S-gene target failure (SGTF).
- BA.2 can likely still be detected by most rapid antigen tests [7].
- There are several significant BA.2 amplicon dropout regions that differ from those identified in BA.1. A summary can be found [here](#).

Protein structures
Kumar et al. have performed a comparative sequence and structural-based computational assessment [5], comparing the following Omicron lineages: BA.1, BA.1.1, BA.2, and BA.3. The authors discuss the predicted effects of multiple shared and unique mutations on spike physio-chemistry, receptor binding, and pathogenicity.

7) SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests
11) SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 37