SARS-CoV-2 Research Summary
Omicron BA.2 Lineage: What do we know?

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	BA.1	BA.2	BA.3
Spike		T19I	
		L24del	
		P25del	
		P26del	
		A27S	
	A67V		A67V
	H69del		H69del
	V70del		V70del
	T95I		T95I
	G142D	**G142D**	**G142D**
	V143del		V143del
	Y144del		Y144del
	Y145del		Y145del
	N211del		N211del
	L212I		L212I
		V213G	
	ins214EPE		
	G339D	**G339D**	**G339D**
	S371L	**S371F**	**S371F**
	S373P	**S373P**	**S373P**
	S375F	**S375F**	**S375F**
		T376A	
		D405N	D405N
		R408S	
	K417N	**K417N**	**K417N**
	N440K	**N440K**	**N440K**
	G446S		G446S
	S477N	**S477N**	**S477N**
	T478K	**T478K**	**T478K**
	E484A	**E484A**	**E484A**
	Q493R	**Q493R**	**Q493R**
	G496S		
	Q498R	**Q498R**	**Q498R**
	N501Y	**N501Y**	**N501Y**
	Y505H	**Y505H**	**Y505H**
	T547K		
	D614G	**D614G**	**D614G**
	H655Y	**H655Y**	**H655Y**
	N679K	**N679K**	**N679K**
	P681H	**P681H**	**P681H**
	N764K	**N764K**	**N764K**
	D796Y	**D796Y**	**D796Y**
	N856K		
	Q954H	**Q954H**	**Q954H**
	N969K	**N969K**	**N969K**
	L981F		

Figure 1: shared (bold) & unique (red) mutations in the spike protein of Omicron sub-lineages.

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 Staten 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).

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		BA.1	BA.2	BA.3
ORF1a	nsp1		S135R	S135R
	nsp3	K38R S1265del L1266I A1892T	T24I G489S	G489S
	nsp4	T492I	L264F T327I L438F T492I	T327I T492I
	nsp5	P132H	P132H	P132H
	nsp6	L105del S106del G107del I189V	S106del G107del F108del	A88V S106del G107del F108del
ORF1b	nsp12	P323L	P323L	P323L
	nsp13		R392C	
	nsp14	I42V	I42V	I42V
	nsp15		T112I	
ORF3a			T223I	T223I
E		T9I	T9I	T9I
M		D3G Q19E A63T	Q19E A63T	Q19E A63T
N		P13L E31del R32del S33del R203K G204R	P13L E31del R32del S33del R203K G204R S413R	P13L E31del R32del S33del R203K G204R S413R

Figure 2: A list of shared (bold) & unique (red) mutations in non-spike regions of Omicron sub-lineages.

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 does 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 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).

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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.

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